Comparative Medicine
Copyright 2008
by the American Association for Laboratory Animal Science

Vol 58, No 4
August 2008
Pages 324–340

The Guinea Pig as a Model of Infectious Diseases

Danielle J Padilla-Carlin,[1] David N McMurray,[2] and Anthony J Hickey[1,*]

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; TGFβ, transforming growth factor β; TNFα, 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 tuberculosis[153] 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)

Received: 30 Oct 2007. Revision requested: 5 Dec 2007. Accepted: 27 Dec 2007.
[1]School of Pharmacy, Division of Molecular Pharmaceutics, University of North Carolina, Chapel Hill, NC; [2]Department of Microbial and Molecular Pathogenesis, College of Medicine, Texas A&M University System Health Science Center, College Station, TX
[*]Corresponding author. Email: ahickey@unc.edu

Table 1. Bacteria studied in the guinea pig

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

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 antiserum[160] 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 Southern[65] 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, Tγ, Tμ, 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 intranasal[141] 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

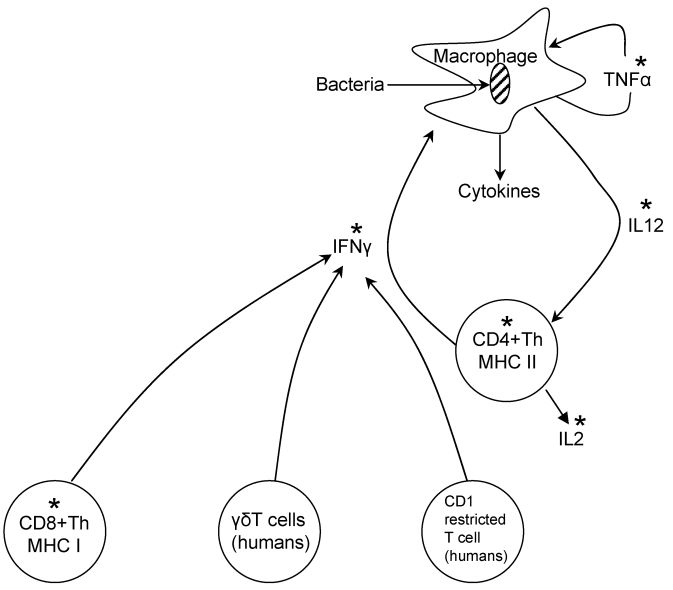

Figure 1. Cascade of immunologic events occurring in the guinea pig model of primary tuberculosis. Antigen presentation occurs by means of the major histocompatability complex (MHC). Similar to the mechanism in humans, *Mycobacterium tuberculosis* (Mtb) bacteria are engulfed by alveolar macrophages. The bacilli, in turn, inhibit phagolysosomal fusion within macrophages. Macrophages produce cytokines (TNFα*, IL1*, IL8[CXCL8]*, IL10*, IL12*, TGFβ*, 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 investigators[29] 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* orthlog,[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 researchers[232] 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 scientists[151] exposed guinea pigs intraperitoneally to low levels of virulent (10^4 CFU) and high levels of avirulent (10^8 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 IL1β, IL4, IL6, IL10, tumor necrosis factor α (TNFα), IFNγ, 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 (TNFα).[63,64] These studies report that TNFα 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 contraceptives[8] 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 protein[17] 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 list[234]).

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 (ID_{50}, 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 production[222]) 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 researchers[300] 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 nonvenereal 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 IL1α, IL2, IL10, IL12p40, TNFα, and transforming growth factor β (TGFβ) 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 IFNγ), 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 cardiolipin (Wasserman) antibodies, an indicator of tissue damage[224,227] (for an alternate view[295]). 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 syphilic 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 increased 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. palladium*. 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 intramuscularly[309] or intraveneously[223] 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 investigators[116] 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 process[142] 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, lidocaine[272]), 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 model[173] 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 antibiotics[147-149] 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 histocompatability.[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 receptor[279] 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 IFNγ 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
IFNγ	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
IL1β	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
TGFβ	Cloned and sequenced	251
	Reverse Transcription-PCR	319
TNFα	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.

References

1. **Adachi S, Hashimoto T, Takeyoshi M, Kato H, Iwata H.** 2006. Development of a monoclonal antibody-based sandwich ELISA for detection of guinea pig interleukin 2. J Vet Med Sci **68:**1281–1287.
2. **Allen SS, Cassone L, Lasco TM, McMurray DN.** 2004. Effect of neutralizing transforming growth factor β1 on the immune response against *Mycobacterium tuberculosis* in guinea pigs. Infect Immun **72:**1358–1363.
3. **Allen SS, McMurray DN.** 2003. Coordinate cytokine gene expression in vivo following induction of tuberculous pleurisy in guinea pigs. Infect Immun **71:**4271–4277.
4. **Antczak DF.** 1982. Structure and function of the major histocompatibility complex in domestic animals. J Am Vet Med Assoc **181:**1030–1036.
5. **Auerbach HS, Lalande ME, Latt S, Colten HR.** 1983. Isolation of guinea pig macrophages bearing surface C4 by fluorescence-activated cell sorting: correlation between surface C4 antigen and C4 protein secretion. J Immunol **131:**2420–2426.
6. **Baker-Zander SA, Hook EW 3rd, Bonin P, Handsfield HH, Lukehart SA.** 1985. Antigens of *Treponema pallidum* recognized by IgG and IgM antibodies during syphilis in humans. J Infect Dis **151:**264–272.
7. **Barron AL, Menna JH, Moses EB, Rank RG, Ryu H, White HJ.** 1989. Response of guinea pigs to intravaginal inoculation with guinea pig cytomegalovirus. Sex Transm Dis **16:**41–46.
8. **Barron AL, Pasley JN, Rank RG, White HJ, Mrak RE.** 1988. Chlamydial salpingitis in female guinea pigs receiving oral contraceptives. Sex Transm Dis **15:**169–173.
9. **Barron AL, White HJ, Rank RG, Soloff BL.** 1979. Target tissues associated with genital infection of female guinea pigs by the chlamydial agent of guinea pig inclusion conjunctivitis. J Infect Dis **139:**60–68.
10. **Bartow RA, McMurray DN.** 1989. Vaccination with *Mycobacterium bovis* BCG affects the distribution of Fc receptor-bearing T lymphocytes in experimental pulmonary tuberculosis. Infect Immun **57:**1374–1379.
11. **Bartow RA, McMurray DN.** 1990. Erythrocyte receptor (CD2)-bearing T lymphocytes are affected by diet in experimental pulmonary tuberculosis. Infect Immun **58:**1843–1847.
12. **Bartow RA, McMurray DN.** 1998. Lymphocytes expressing Fc gamma receptors suppress antigen-induced proliferation in cells from guinea pigs infected with virulent *Mycobacterium tuberculosis*. Cell Immunol **184:**51–57.
13. **Basaraba RJ, Dailey DD, McFarland CT, Shanley CA, Smith EE, McMurray DN, Orme IM.** 2006. Lymphadenitis as a major element of disease in the guinea pig model of tuberculosis. Tuberculosis (Edinb) **86:**386–394.
14. **Baskerville A, Conlan JW, Ashworth LA, Dowsett AB.** 1986. Pulmonary damage caused by a protease from *Legionella pneumophila*. Br J Exp Pathol **67:**527–536.
15. **Baskerville A, Fitzgeorge RB, Broster M, Hambleton P, Dennis PJ.** 1981. Experimental transmission of Legionnaires' disease by exposure to aerosols of *Legionella pneumophila*. Lancet **2:**1389–1390.
16. **Batteiger BE, Rank RG.** 1987. Analysis of the humoral immune response to chlamydial genital infection in guinea pigs. Infect Immun **55:**1767–1773.
17. **Batteiger BE, Rank RG, Bavoil PM, Soderberg LS.** 1993. Partial protection against genital reinfection by immunization of guinea pigs with isolated outer-membrane proteins of the chlamydial agent of guinea-pig inclusion conjunctivitis. J Gen Microbiol **139:**2965–2972.
18. **Baughn RE.** 1986. Antibody-independent interactions of fibronectin, C1q, and human neutrophils with *Treponema pallidum*. Infect Immun **54:**456–464.
19. **Baughn RE, McNeely MC, Jorizzo JL, Musher DM.** 1986. Characterization of the antigenic determinants and host components in immune complexes from patients with secondary syphilis. J Immunol **136:**1406–1414.
20. **Baughn RE, Wicher V, Jakubowski A, Wicher K.** 1987. Humoral response in *Treponema pallidum*-infected guinea pigs. II. Circulating immune complexes and autoimmune responses. J Immunol **138:**4435–4440.
21. **Baughn RE, Wicher V, Wicher K.** 1992. Production of rheumatoid factor in adoptively immune guinea pigs after challenge with *Treponema pallidum*. Immunology **76:**548–552.
22. **Berendt RF, Young HW, Allen RG, Knutsen GL.** 1980. Dose–response of guinea pigs experimentally infected with aerosols of *Legionella pneumophila*. J Infect Dis **141:**186–192.
23. **Berger KH, Merriam JJ, Isberg RR.** 1994. Altered intracellular targeting properties associated with mutations in the *Legionella pneumophila dotA* gene. Mol Microbiol **14:**809–822.
24. **Bitter-Suermann D, Hoffmann T, Burger R, Hadding U.** 1981. Linkage of total deficiency of the second component (C2) of the complement system and of genetic C2 polymorphism to the major histocompatibility complex of the guinea pig. J Immunol **127:**608–612.
25. **Bjornson AB, Bjornson HS, Lincoln NA, Altemeier WA.** 1984. Relative roles of burn injury, wound colonization, and wound infection in induction of alterations of complement function in a guinea pig model of burn injury. J Trauma **24:**106–115.
26. **Blander SJ, Horwitz MA.** 1989. Vaccination with the major secretory protein of *Legionella pneumophila* induces cell-mediated and protective immunity in a guinea pig model of Legionnaires' disease. J Exp Med **169:**691–705.
27. **Blander SJ, Horwitz MA.** 1991. Vaccination with *Legionella pneumophila* membranes induces cell-mediated and protective immunity in a guinea pig model of Legionnaires' disease. Protective immunity independent of the major secretory protein of *Legionella pneumophila*. J Clin Invest **87:**1054–1059.
28. **Blander SJ, Horwitz MA.** 1993. Major cytoplasmic membrane protein of *Legionella pneumophila*, a genus common antigen and member of the hsp 60 family of heat shock proteins, induces protective immunity in a guinea pig model of Legionnaires' disease. J Clin Invest **91:**717–723.
29. **Blander SJ, Szeto L, Shuman HA, Horwitz MA.** 1990. An immunoprotective molecule, the major secretory protein of *Legionella pneumophila*, is not a virulence factor in a guinea pig model of Legionnaires' disease. J Clin Invest **86:**817–824.
30. **Blaser J, Vergeres P, Widmer AF, Zimmerli W.** 1995. In vivo verification of in vitro model of antibiotic treatment of device-related infection. Antimicrob Agents Chemother **39:**1134–1139.
31. **Bluestein HG, Ellman L, Green I, Benacerraf B.** 1971. Specific immune response genes of the guinea pig. 3. Linkage of the GA and GT immune response genes to histocompatibility genotypes in inbred guinea pigs. J Exp Med **134:**1529–1537.
32. **Bluestein HG, Green I, Benacerraf B.** 1971. Specific immune response genes of the guinea pig. I. Dominant genetic control of immune responsiveness to copolymers of L-glutamic acid and L-alanine and L-glutamic acid and L-tyrosine. J Exp Med **134:**458–470.
33. **Bluestein HG, Green I, Benacerraf B.** 1971. Specific immune response genes of the guinea pig. II. Relationship between the poly-

L-lysine gene and the genes controlling immune responsiveness to copolymers of L-glutamic acid and L-alanine and L-glutamic acid and L-tyrosine in random-bred Hartley guinea pigs. J Exp Med **134:**471–481.

34. **Bluestein HG, Green I, Maurer PH, Benacerraf B.** 1972. Specific immune response genes of the guinea pig. V. Influence of the GA and GT immune response genes on the specificity of cellular and humoral immune responses to a terpolymer of L-glutamic acid, L-alanine, and L-tyrosine. J Exp Med **135:**98–109.
35. **Boon RJ, Beale AS, Sutherland R.** 1985. Efficacy of topical mupirocin against an experimental *Staphylococcus aureus* surgical wound infection. J Antimicrob Chemother **16:**519–526.
36. **Bos JD, Hamerlinck F, Cormane RH.** 1980. Antitreponemal IgE in early syphilis. Br J Vener Dis **56:**20–25.
37. **Bouchenaki N, Vaudaux PE, Huggler E, Waldvogel FA, Lew DP.** 1990. Successful single-dose prophylaxis of *Staphylococcus aureus* foreign body infections in guinea pigs by fleroxacin. Antimicrob Agents Chemother **34:**21–24.
38. **Brade V, Cook CT, Shin HS, Mayer MM.** 1972. Studies on the properdin system: isolation of a heat-labile factor from guinea pig serum related to a human glycine-rich β glycoprotein (GBG or factor B). J Immunol **109:**1174–1181.
39. **Brade V, Nicholson A, Lee GD, Mayer MM.** 1974. The reaction of zymosan with the properdin system: isolation of purified factor D from guinea pig serum and study of its reaction characteristics. J Immunol **112:**1845–1854.
40. **Breiman RF, Horwitz MA.** 1987. Guinea pigs sublethally infected with aerosolized *Legionella pneumophila* develop humoral and cell-mediated immune responses and are protected against lethal aerosol challenge. A model for studying host defense against lung infections caused by intracellular pathogens. J Exp Med **165:**799–811.
41. **Burger R, Clement L, Schroer J, Chiba J, Shevach EM.** 1981. Monoclonal antibodies to guinea pig Ia antigens. I. Production, serologic, and immunochemical characterization. J Immunol **126:**32–37.
42. **Burger R, Reske K, Mauer U, von Steldern D, Husmann M.** 1983. Identification and characterization of gp TFA1, a guinea pig T cell surface antigen associated with T cell function. J Immunol **131:**1350–1355.
43. **Burger R, Scher I, Sharrow SO, Shevach EM.** 1984. Nonactivated guinea pig T cells and thymocytes express Ia antigens: FACS analysis with alloantibodies and monoclonal antibodies. Immunology **51:**93–102.
44. **Burger R, Schrod L, Schaefer H.** 1986. Functionally relevant membrane proteins of human and guinea-pig T lymphocytes. Mol Immunol **23:**1149–1156.
45. **Burger R, Shevach EM.** 1980. Monoclonal antibodies to guinea pig Ia antigens. II. Effect on alloantigen-, antigen-, and mitogen-induced T lymphocyte proliferation in vitro. J Exp Med **152:**1011–1023.
46. **Cagni A, Chuard C, Vaudaux PE, Schrenzel J, Lew DP.** 1995. Comparison of sparfloxacin, temafloxacin, and ciprofloxacin for prophylaxis and treatment of experimental foreign-body infection by methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **39:**1655–1660.
47. **Campbell EM, Proudfoot AE, Yoshimura T, Allet B, Wells TN, White AM, Westwick J, Watson ML.** 1997. Recombinant guinea pig and human RANTES activate macrophages but not eosinophils in the guinea pig. J Immunol **159:**1482–1489.
48. **Catusse J, Faye P, Loillier B, Cremers B, Franck RM, Luccarini JM, Pruneau D, Paquet JL.** 2003. Cloning and characterization of guinea pig interleukin 8 receptor. Biochem Pharmacol **66:**1171–1180.
49. **Cegielski JP, McMurray DN.** 2004. The relationship between malnutrition and tuberculosis: evidence from studies in humans and experimental animals. Int J Tuberc Lung Dis **8:**286–298.
50. **Chiba J, Egashira Y.** 1978. Specific immune response genes of new inbred strains of guinea pigs. Jpn J Med Sci Biol **31:**425–430.
51. **Chiba J, Otokawa M, Nakagawa M, Egashira Y.** 1978. Serological studies on the major histocompatibility complex of new inbred strains of the guinea pig. Microbiol Immunol **22:**545–555.
52. **Cho H, Lasco TM, Allen SS, Yoshimura T, McMurray DN.** 2005. Recombinant guinea pig tumor necrosis factor alpha stimulates the expression of interleukin 12 and the inhibition of *Mycobacterium tuberculosis* growth in macrophages. Infect Immun **73:**1367–1376.
53. **Cho H, McMurray DN.** 2005. Neutralization of tumor necrosis factor α suppresses antigen-specific type 1 cytokine responses and reverses the inhibition of mycobacterial survival in cocultures of immune guinea pig T lymphocytes and infected macrophages. Infect Immun **73:**8437–8441.
54. **Cho H, McMurray DN.** 2007. Recombinant guinea pig TNFα enhances antigen-specific type 1 T lymphocyte activation in guinea pig splenocytes. Tuberculosis (Edinb) **87:**87–93.
55. **Chuard C, Rohner P, Dunand V, Auckenthaler R, Lew DP.** 1992. In vitro and in vivo evaluation of the antistaphylococcal activity of S-5556, a new 16-membered macrolide. J Antimicrob Chemother **30:**327–337.
56. **Claman HN.** 1972. Corticosteroids and lymphoid cells. N Engl J Med **287:**388–397.
57. **Conlan JW, Baskerville A, Ashworth LA.** 1986. Separation of *Legionella pneumophila* proteases and purification of a protease which produces lesions like those of Legionnaires' disease in guinea pig lung. J Gen Microbiol **132:**1565–1574.
58. **Costerton JW, Geesey GG, Cheng KJ.** 1978. How bacteria stick. Sci Am **238:**86–95.
59. **Cutler RR.** 1979. Relationship between antibiotic resistance, the production of 'virulence factors', and virulence for experimental animals in Staphylococcus aureus. J Med Microbiol **12:**55–62.
60. **D'Erchia AM, Gissi C, Pesole G, Saccone C, Arnason U.** 1996. The guinea pig is not a rodent. Nature **381:**597–600.
61. **Dai G, McMurray DN.** 1998. Altered cytokine production and impaired antimycobacterial immunity in protein-malnourished guinea pigs. Infect Immun **66:**3562–3568.
62. **Dannenberg AM Jr, Rook GAW.** 1994. Pathogenesis of pulmonary tuberculosis: an interplay of tissue-damaging and macrophage activating immune responses-dual mechanisms that control bacillary multiplication. In: Bloom BR, editor. Tuberculosis: pathogenesis, protection, and control. Washington (DC): American Society for Microbiology.
63. **Darville T, Andrews CW Jr, Rank RG.** 2000. Does inhibition of tumor necrosis factor α affect chlamydial genital tract infection in mice and guinea pigs? Infect Immun **68:**5299–5305.
64. **Darville T, Laffoon KK, Kishen LR, Rank RG.** 1995. Tumor necrosis factor α activity in genital tract secretions of guinea pigs infected with chlamydiae. Infect Immun **63:**4675–4681.
65. **Dascher CC, Hiromatsu K, Naylor JW, Brauer PP, Brown KA, Storey JR, Behar SM, Kawasaki ES, Porcelli SA, Brenner MB, LeClair KP.** 1999. Conservation of a CD1 multigene family in the guinea pig. J Immunol **163:**5478–5488.
66. **Davis GS, Winn CW Jr, Gump DW, Craighead JM, Beaty HN.** 1983. Legionnaires' pneumonia in guinea pigs and rats produced by aerosol exposure. Chest **83:**15S–16S.
67. **Davis GS, Winn WC Jr, Gump DW, Beaty HN.** 1983. The kinetics of early inflammatory events during experimental pneumonia due to *Legionella pneumophila* in guinea pigs. J Infect Dis **148:**823–835.
68. **Davis GS, Winn WC Jr, Gump DW, Craighead JE, Beaty HN.** 1982. Legionnaires' pneumonia after aerosol exposure in guinea pigs and rats. Am Rev Respir Dis **126:**1050–1057.
69. **Donlan RM.** 2001. Biofilms and device-associated infections. Emerg Infect Dis **7:**277–281.
70. **Dournon E, Rajagopalan P**. 1988. Comparison of spiramycin and erythromycin in the treatment of experimental guinea pig legionellosis. J Antimicrob Chemother **22 Suppl B:**69–72.
71. **Dournon E, Rajagopalan P, Vilde JL, Pocidalo JJ**. 1986. Efficacy of pefloxacin in comparison with erythromycin in the treatment of experimental guinea pig legionellosis. J Antimicrob Chemother **17 Suppl B:**41–48.
72. **Edelstein PH.** 1991. Rifampin resistance of *Legionella pneumophila* is not increased during therapy for experimental Legionnaires disease:

study of rifampin resistance using a guinea pig model of Legionnaires disease. Antimicrob Agents Chemother **35:**5–9.
73. **Edelstein PH.** 1995. Antimicrobial chemotherapy for Legionnaires' disease: a review. Clin Infect Dis **21 Suppl 3:**S265–S276.
74. **Edelstein PH.** 1995. Review of azithromycin activity against *Legionella* spp. Pathol Biol (Paris) **43:**569–572.
75. **Edelstein PH, Beer KB, DeBoynton ED.** 1987. Influence of growth temperature on virulence of *Legionella pneumophila*. Infect Immun **55:**2701–2705.
76. **Edelstein PH, Edelstein MA, Higa F, Falkow S.** 1999. Discovery of virulence genes of *Legionella pneumophila* by using signature tagged mutagenesis in a guinea pig pneumonia model. Proc Natl Acad Sci USA **96:**8190–8195.
77. **Edelstein PH, Hu B, Higa F, Edelstein MA.** 2003. lvgA, a novel *Legionella pneumophila* virulence factor. Infect Immun **71:**2394–2403.
78. **Edelstein PH, Snitzer JB, Finegold SM.** 1982. Isolation of *Legionella pneumophila* from hospital potable water specimens: comparison of direct plating with guinea pig inoculation. J Clin Microbiol **15:**1092–1096.
79. **Edlich RF, Tsung MS, Rogers W, Rogers P, Wangensteen OH.** 1968. Studies in management of the contaminated wound. I. Technique of closure of such wounds together with a note on a reproducible experimental model. J Surg Res **8:**585–592.
80. **Eisenstein TK, Tamada R, Meissler J, Flesher A, Oels HC.** 1984. Vaccination against *Legionella pneumophila*: serum antibody correlates with protection induced by heat-killed or acetone-killed cells against intraperitoneal but not aerosol infection in guinea pigs. Infect Immun **45:**685–691.
81. **Elliott JA, Johnson W, Helms CM.** 1981. Ultrastructural localization and protective activity of a high-molecular-weight antigen isolated from *Legionella pneumophila*. Infect Immun **31:**822–824.
82. **Ellman L, Green I, Frank M.** 1970. Genetically controlled total deficiency of the fourth component of complement in the guinea pig. Science **170:**74–75.
83. **Ellman L, Green I, Martin WJ, Benacerraf B.** 1970. Linkage between the poly-L-lysine gene and the locus controlling the major histocompatibility antigens in strain 2 guinea pigs. Proc Natl Acad Sci USA **66:**322–328.
84. **Espevik T, Nissen-Meyer J.** 1986. A highly sensitive cell line, WEHI 164 clone 13, for measuring cytotoxic factor/tumor necrosis factor from human monocytes. J Immunol Methods **95:**99–105.
85. **Falcieri E, Vaudaux P, Huggler E, Lew D, Waldvogel F.** 1987. Role of bacterial exopolymers and host factors on adherence and phagocytosis of *Staphylococcus aureus* in foreign body infection. J Infect Dis **155:**524–531.
86. **Farshy CE, Cruce DD, Klein GC, Wilkinson HW, Feeley JC.** 1979. Immunoglobulin specificity of the microagglutination test for the Legionnaires' disease bacterium. Ann Intern Med **90:**690.
87. **Fields BS, Barbaree JM, Shotts EB Jr, Feeley JC, Morrill WE, Sanden GN, Dykstra MJ.** 1986. Comparison of guinea pig and protozoan models for determining virulence of *Legionella* species. Infect Immun **53:**553–559.
88. **Fitzgerald KA, Palsson-McDermott EM, Bowie AG, Jefferies CA, Mansell AS, Brady G, Brint E, Dunne A, Gray P, Harte MT, McMurray D, Smith DE, Sims JE, Bird TA, O'Neill LA.** 2001. Mal (MyD88-adapter-like) is required for Toll-like receptor-4 signal transduction. Nature **413:**78–83.
89. **Fluckiger U, Ulrich M, Steinhuber A, Doring G, Mack D, Landmann R, Goerke C, Wolz C.** 2005. Biofilm formation, icaADBC transcription, and polysaccharide intercellular adhesin synthesis by staphylococci in a device-related infection model. Infect Immun **73:**1811–1819.
90. **Foster TJ, Hook M.** 1998. Surface protein adhesins of *Staphylococcus aureus*. Trends Microbiol **6:**484–488.
91. **Francois P, Tu Quoc PH, Bisognano C, Kelley WL, Lew DP, Schrenzel J, Cramton SE, Gotz F, Vaudaux P.** 2003. Lack of biofilm contribution to bacterial colonisation in an experimental model of foreign body infection by Staphylococcus aureus and Staphylococcus epidermidis. FEMS Immunol Med Microbiol **35:**135–140.
92. **Frank MM.** 1995. Animal models for complement deficiencies. J Clin Immunol **15:**113S–121S.
93. **Freedman AP, Katz SM.** 1981. The prevalence of serum antibodies to *Legionella pneumophila* in patients with chronic pulmonary disease. Am Rev Respir Dis **123:**238–239.
94. **Friedman H, Widen R, Lee I, Klein T.** 1983. Cellular immunity to *Legionella pneumophila* in guinea pigs assessed by direct and indirect migration inhibition reactions in vitro. Infect Immun **41:**1132–1137.
95. **Friedman H, Yamamoto Y, Klein TW.** 2002. *Legionella pneumophila* pathogenesis and immunity. Semin Pediatr Infect Dis **13:**273–279.
96. **Galandiuk S, Wrightson WR, Young S, Myers S, Polk HC Jr.** 1997. Absorbable, delayed-release antibiotic beads reduce surgical wound infection. Am Surg **63:**831–835.
97. **Ganguly R, Durieux MF, Waldman RH.** 1976. Macrophage function in vitamin C-deficient guinea pigs. Am J Clin Nutr **29:**762–765.
98. **Garcia-Contreras L, Sethuraman V, Kazantseva M, Godfrey V, Hickey AJ.** 2006. Evaluation of dosing regimen of respirable rifampicin biodegradable microspheres in the treatment of tuberculosis in the guinea pig. J Antimicrob Chemother **58:**980–986.
99. **Geczy A, de Weck AL.** 1974. Proceedings: genetic control of sensitization to chemically defined antigens and its relationship to histocompatibility antigens in guinea pigs. Monogr Allergy **8:**83–88.
100. **Geczy AF.** 1977. Histocompatibility antigens and genetic control of the immune response in guinea pigs IV. Specific inhibition of lymphocyte proliferation by auto-anti-idiotypic antibodies. J Exp Med **145:**1093–1098.
101. **Geczy AF, de Weck AL, Schwartz BD, Shevach EM.** 1975. The major histocompatibility complex of the guinea pig. I. Serologic and genetic studies. J Immunol **115:**1704–1710.
102. **Geisbrecht BV, Nikonenko B, Samala R, Nakamura R, Nacy CA, Sacksteder KA.** 2006. Design and optimization of a recombinant system for large-scale production of the MPT64 antigen from *Mycobacterium tuberculosis*. Protein Expr Purif **46:**64–72.
103. **Gell PG, Benacerraf B.** 1961. Studies on hypersensitivity. IV. The relationship between contact and delayed sensitivity: a study of the specificity of cellular immune reactions. J Exp Med **113:**571–585.
104. **Goerke C, Fluckiger U, Steinhuber A, Zimmerli W, Wolz C.** 2001. Impact of the regulatory loci agr, sarA and sae of Staphylococcus aureus on the induction of α toxin during device-related infection resolved by direct quantitative transcript analysis. Mol Microbiol **40:**1439–1447.
105. **Gold HS, Moellering RC Jr.** 1996. Antimicrobial drug resistance. N Engl J Med **335:**1445–1453.
106. **Golden MR, Schillinger JA, Markowitz L, St Louis ME.** 2000. Duration of untreated genital infections with *Chlamydia trachomatis*: a review of the literature. Sex Transm Dis **27:**329–337.
107. **Gonzalez-Juarrero M, Turner OC, Turner J, Marietta P, Brooks JV, Orme IM.** 2001. Temporal and spatial arrangement of lymphocytes within lung granulomas induced by aerosol infection with *Mycobacterium tuberculosis*. Infect Immun **69:**1722–1728.
108. **Graur D, Hide WA, Li WH.** 1991. Is the guinea pig a rodent? Nature **351:**649–652.
109. **Green I, Inman JK, Benacerraf B.** 1970. Genetic control of the immune response of guinea pigs to limiting doses of bovine serum albumin: relationship to the poly-L-lysine gene. Proc Natl Acad Sci USA **66:**1267–1274.
110. **Green I, Paul WE, Benacerraf B.** 1967. A study of the passive transfer of delayed hypersensitivity to DNP-poly-L-lysine and DNP-GL in responder and nonresponder guinea pigs. J Exp Med **126:**959–967.
111. **Green RL, Scales RW, Kraus SJ.** 1976. Increased serum immunoglobulin E concentrations in venereal diseases. Br J Vener Dis **52:**257–260.
112. **Hambleton P, Bailey NE, Fitzgeorge RB, Baskerville A.** 1985. Clinical chemical responses to experimental airborne legionellosis in the guinea pig. Br J Exp Pathol **66:**173–183.

113. **Hamuro J, Hadding U, Bitter-Suermann D.** 1978. Fragments Ba and Bb derived from guinea pig factor B of the properdin system: purification, characterization, and biologic activities. J Immunol **120:**438–444.
114. **Harvard BIoMa** [Internet]. Index of /ftp/pub/assemblies/mammals/guineaPig/cavPor3. Cambridge (MA): MIT [updated 2008 Feb 12; cited 2008 July 23]. Available from: http://www.broad.mit.edu/ftp/pub/assemblies/mammals/guineaPig/cavPor3/.
115. **Haslov K, Andersen A, Nagai S, Gottschau A, Sorensen T, Andersen P.** 1995. Guinea pig cellular immune responses to proteins secreted by *Mycobacterium tuberculosis*. Infect Immun **63:**804–810.
116. **Herndon DN, Wilmore DW, Mason AD Jr.** 1978. Development and analysis of a small animal model simulating the human postburn hypermetabolic response. J Surg Res **25:**394–403.
117. **Higa F, Edelstein PH.** 2001. Potential virulence role of the *Legionella pneumophila* ptsP ortholog. Infect Immun **69:**4782–4789.
118. **Higashi N, Yoshizuka N, Kobayashi Y.** 1995. Phenotypic properties and cytokine production of skin-infiltrating cells obtained from guinea pig delayed-type hypersensitivity reaction sites. Cell Immunol **164:**28–35.
119. **Higashi N, Yoshizuka N, Ohuchi A, Osawa T, Kobayashi Y.** 1995. Involvement of inflammatory cytokines in a delayed-type hypersensitivity reaction. Cell Immunol **161:**288–294.
120. **Hiromatsu K, Dascher CC, LeClair KP, Sugita M, Furlong ST, Brenner MB, Porcelli SA.** 2002. Induction of CD1-restricted immune responses in guinea pigs by immunization with mycobacterial lipid antigens. J Immunol **169:**330–339.
121. **Hiromatsu K, Dascher CC, Sugita M, Gingrich-Baker C, Behar SM, LeClair KP, Brenner MB, Porcelli SA.** 2002. Characterization of guinea-pig group 1 CD1 proteins. Immunology **106:**159–172.
122. **Horikawa T, Komohara Y, Kiyota E, Terasaki Y, Takagi K, Takeya M.** 2006. Detection of guinea pig macrophages by a new CD68 monoclonal antibody, PM-1K. J Mol Histol **37:**15–25.
123. **Horwitz MA.** 1983. Cell-mediated immunity in Legionnaires' disease. J Clin Invest **71:**1686–1697.
124. **Horwitz MA.** 1983. The Legionnaires' disease bacterium (*Legionella pneumophila*) inhibits phagosome-lysosome fusion in human monocytes. J Exp Med **158:**2108–2126.
125. **Horwitz MA, Maxfield FR.** 1984. *Legionella pneumophila* inhibits acidification of its phagosome in human monocytes. J Cell Biol **99:**1936–1943.
126. **Horwitz MA, Silverstein SC.** 1980. Legionnaires' disease bacterium (*Legionella pneumophila*) multiples intracellularly in human monocytes. J Clin Invest **66:**441–450.
127. **Howard LV, O'Leary MP, Nichols RL.** 1976. Animal model studies of genital chlamydial infections. Immunity to reinfection with guinea pig inclusion conjunctivitis agent in the urethra and eye of male guinea pigs. Br J Vener Dis **52:**261–265.
128. **Howell JM, Bresnahan KA, Stair TO, Dhindsa HS, Edwards BA.** 1995. Comparison of effects of suture and cyanoacrylate tissue adhesive on bacterial counts in contaminated lacerations. Antimicrob Agents Chemother **39:**559–560.
129. **Howell JM, Dhindsa HS, Stair TO, Edwards BA.** 1993. Effect of scrubbing and irrigation on staphylococcal and streptococcal counts in contaminated lacerations. Antimicrob Agents Chemother **37:**2754–2755.
130. **Howell JM, Stair TO, Howell AW, Mundt DJ, Falcone A, Peters SR.** 1993. The effect of scrubbing and irrigation with normal saline, povidone iodine, and cefazolin on wound bacterial counts in a guinea pig model. Am J Emerg Med **11:**134–138.
131. **Husmann LK, Johnson W.** 1992. Adherence of *Legionella pneumophila* to guinea pig peritoneal macrophages, J774 mouse macrophages, and undifferentiated U937 human monocytes: role of Fc and complement receptors. Infect Immun **60:**5212–5218.
132. **Husmann LK, Johnson W.** 1994. Cytotoxicity of extracellular *Legionella pneumophila*. Infect Immun **62:**2111–2114.
133. **Igietseme JU, Rank RG.** 1991. Susceptibility to reinfection after a primary chlamydial genital infection is associated with a decrease of antigen-specific T cells in the genital tract. Infect Immun **59:**1346–1351.
134. **Imamura T, Tanase S, Szmyd G, Kozik A, Travis J, Potempa J.** 2005. Induction of vascular leakage through release of bradykinin and a novel kinin by cysteine proteinases from *Staphylococcus aureus*. J Exp Med **201:**1669–1676.
135. **Jakubowski A, Wicher V, Gruhn R, Wicher K.** 1987. Natural antibodies to treponemal antigens in four strains of guinea pigs. Immunology **60:**281–285.
136. **Jeevan A, McFarland CT, Yoshimura T, Skwor T, Cho H, Lasco T, McMurray DN.** 2006. Production and characterization of guinea pig recombinant gamma interferon and its effect on macrophage activation. Infect Immun **74:**213–224.
137. **Jeevan A, Yoshimura T, Foster G, McMurray DN.** 2002. Effect of *Mycobacterium bovis* BCG vaccination on interleukin 1β and RANTES mRNA expression in guinea pig cells exposed to attenuated and virulent mycobacteria. Infect Immun **70:**1245–1253.
138. **Jeevan A, Yoshimura T, Lee KE, McMurray DN.** 2003. Differential expression of gamma interferon mRNA induced by attenuated and virulent Mycobacterium tuberculosis in guinea pig cells after Mycobacterium bovis BCG vaccination. Infect Immun **71:**354–364.
139. **Kaiser AB, Kernodle DS.** 1998. Synergism between poly-(1-6)-β-D-glucopyranosyl-(1-3)-β-D-glucopyranose glucan and cefazolin in prophylaxis of staphylococcal wound infection in a guinea pig model. Antimicrob Agents Chemother **42:**2449–2451.
140. **Kaiser AB, Kernodle DS, Parker RA.** 1992. Low-inoculum model of surgical wound infection. J Infect Dis **166:**393–399.
141. **Katz SM, Habib WA, Hammel JM, Nash P.** 1982. Lack of airborne spread of infection by *Legionella pneumophila* among guinea pigs. Infect Immun **38:**620–622.
142. **Kaufman T, Lusthaus SN, Sagher U, Wexler MR.** 1990. Deep partial skin thickness burns: a reproducible animal model to study burn wound healing. Burns **16:**13–16.
143. **Kawabata TT, Babcock LS, Gauggel DL, Asquith TN, Fletcher ER, Horn PA, Ratajczak HV, Graziano FM.** 1995. Optimization and validation of an ELISA to measure specific guinea pig IgG1 antibody as an alternative to the in vivo passive cutaneous anaphylaxis assay. Fundam Appl Toxicol **24:**238–246.
144. **Kawahara M, Nakasone T, Honda M.** 2002. Dynamics of gamma interferon, interleukin-12 (IL-12), IL-10, and transforming growth factor beta mRNA expression in primary *Mycobacterium bovis* BCG infection in guinea pigs measured by a real-time fluorogenic reverse transcription-PCR assay. Infect Immun **70:**6614–6620.
145. **Kawai K, Suzuki S, Tabata Y, Taira T, Ikada Y, Nishimura Y.** 2001. Development of an artificial dermis preparation capable of silver sulfadiazine release. J Biomed Mater Res **57:**346–356.
146. **Kernodle DS, Gates H, Kaiser AB.** 1998. Prophylactic antiinfective activity of poly-[1-6]-β-D-glucopyranosyl-[1-3]-β-D-glucopryanose glucan in a guinea pig model of staphylococcal wound infection. Antimicrob Agents Chemother **42:**545–549.
147. **Kernodle DS, Kaiser AB.** 1993. Comparative prophylactic efficacy of cefazolin and vancomycin in a guinea pig model of *Staphylococcus aureus* wound infection. J Infect Dis **168:**152–157.
148. **Kernodle DS, Kaiser AB.** 1993. Efficacy of prophylaxis with β-lactams and β-lactam-β-lactamase inhibitor combinations against wound infection by methicillin-resistant and borderline-susceptible *Staphylococcus aureus* in a guinea pig model. Antimicrob Agents Chemother **37:**702–707.
149. **Kernodle DS, Kaiser AB.** 1994. Comparative prophylactic efficacies of ciprofloxacin, ofloxacin, cefazolin, and vancomycin in experimental model of staphylococcal wound infection. Antimicrob Agents Chemother **38:**1325–1330.
150. **Kessler CM, Tang Z, Jacobs HM, Szymanski LM.** 1997. The suprapharmacologic dosing of antithrombin concentrate for *Staphylococcus aureus*-induced disseminated intravascular coagulation in guinea pigs: substantial reduction in mortality and morbidity. Blood **89:**4393–4401.

151. **Klein TW, Friedman H, Widen R.** 1984. Relative potency of virulent versus avirulent *Legionella pneumophila* for induction of cell-mediated immunity. Infect Immun **44:**753–755.
152. **Klunner T, Bartels T, Vordermeier M, Burger R, Schafer H.** 2001. Immune reactions of CD4- and CD8-positive T cell subpopulations in spleen and lymph nodes of guinea pigs after vaccination with Bacillus Calmette Guerin. Vaccine **19:**1968–1977.
153. **Koch R.** 1882. Aetiologie der Tuberculose. Berlin Klin Wochenschr **19:**221–230.
154. **Kraal G, Shiamatey-Koolma R, Hoffer M, Baker D, Scheper R.** 1988. Histochemical identification of guinea pig macrophages by monoclonal antibody MR1. Immunology **65:**523–528.
155. **Kraal G, Twisk A, Tan B, Scheper R.** 1986. A surface molecule on guinea pig lymphocytes involved in adhesion and homing. Eur J Immunol **16:**1515–1519.
156. **Lafond RE, Lukehart SA.** 2006. Biological basis for syphilis. Clin Microbiol Rev **19:**29–49.
157. **Lamm ME, Lisowska-Bernstein B, Green I, Benacerraf B.** 1968. Peptide mapping study of anti-DNP-PLL antibodies produced by guinea pigs with and without the *PLL* gene. Proc Soc Exp Biol Med **127:**1139–1141.
158. **Lammers R, Henry C, Howell J.** 2001. Bacterial counts in experimental, contaminated crush wounds irrigated with various concentrations of cefazolin and penicillin. Am J Emerg Med **19:**1–5.
159. **Lamont HC, Semine DZ, Leveille C, Nichols RL.** 1978. Immunity to vaginal reinfection in female guinea pigs infected sexually with *Chlamydia* of guinea pig inclusion conjunctivitis. Infect Immun **19:**807–813.
160. **Lasco TM, Cassone L, Kamohara H, Yoshimura T, McMurray DN.** 2005. Evaluating the role of tumor necrosis factor α in experimental pulmonary tuberculosis in the guinea pig. Tuberculosis (Edinb) **85:**245–258.
161. **Lasco TM, Turner OC, Cassone L, Sugawara I, Yamada H, McMurray DN, Orme IM.** 2004. Rapid accumulation of eosinophils in lung lesions in guinea pigs infected with *Mycobacterium tuberculosis*. Infect Immun **72:**1147–1149.
162. **Levine BB, Ojeda A, Benacerraf B.** 1963. Basis for the antigenicity of hapten–poly-L-lysine conjugates in random-bred guinea pigs. Nature **200:**544–546.
163. **Levine BB, Ojeda A, Benacerraf B.** 1963. Studies on artificial antigens. III. The genetic control of the immune response to hapten–poly-L-lysine conjugates in guinea pigs. J Exp Med **118:**953–957.
164. **Limb GA, Brown KA, Wolstencroft RA, Ellis BA, Dumonde DC.** 1988. Modulation of Fc and C3b receptor expression on guinea pig macrophages by lymphokines. Clin Exp Immunol **74:**171–176.
165. **Lowy FD.** 1998. *Staphylococcus aureus* infections. N Engl J Med **339:**520–532.
166. **Luneberg E, Zahringer U, Knirel YA, Steinmann D, Hartmann M, Steinmetz I, Rohde M, Kohl J, Frosch M.** 1998. Phase-variable expression of lipopolysaccharide contributes to the virulence of *Legionella pneumophila*. J Exp Med **188:**49–60.
167. **Lyons MJ, Yoshimura T, McMurray DN.** 2002. *Mycobacterium bovis* BCG vaccination augments interleukin 8 mRNA expression and protein production in guinea pig alveolar macrophages infected with *Mycobacterium tuberculosis*. Infect Immun **70:**5471–5478.
168. **Lyons MJ, Yoshimura T, McMurray DN.** 2004. Interleukin (IL) 8 (CXCL8) induces cytokine expression and superoxide formation by guinea pig neutrophils infected with *Mycobacterium tuberculosis*. Tuberculosis (Edinb) **84:**283–292.
169. **Mainali ES, McMurray DN.** 1998. Protein deficiency induces alterations in the distribution of T-cell subsets in experimental pulmonary tuberculosis. Infect Immun **66:**927–931.
170. **Maiwald M, Schill M, Stockinger C, Helbig JH, Luck PC, Witzleb W, Sonntag HG.** 1995. Detection of *Legionella* DNA in human and guinea pig urine samples by the polymerase chain reaction. Eur J Clin Microbiol Infect Dis **14:**25–33.
171. **Mauer-Gross U, von Steldern D, Hadding U, Bitter-Suermann D, Burger R.** 1985. Cell surface antigens on the guinea-pig macrophage: identification by monoclonal antibodies and association with the activation state. Immunology **55:**519–530.
172. **Maurin M, Lepidi H, La Scola B, Feuerstein M, Andre M, Pellissier JF, Raoult D.** 1997. Guinea pig model for *Staphylococcus aureus* native valve endocarditis. Antimicrob Agents Chemother **41:**1815–1817.
173. **Mazurak VC, Burrell RE, Tredget EE, Clandinin MT, Field CJ.** 2007. The effect of treating infected skin grafts with Acticoat on immune cells. Burns **33:**52–58.
174. **McBride BW, Newell DG.** 1989. Production and characterization of monoclonal antibodies directed against guinea pig IgG subclasses. J Immunol Methods **118:**193–198.
175. **McDade JE, Shepard CC.** 1979. Virulent to avirulent conversion of Legionnaires' disease bacterium (*Legionella pneumophila*)::its effect on isolation techniques. J Infect Dis **139:**707–711.
176. **McDade JE, Shepard CC, Fraser DW, Tsai TR, Redus MA, Dowdle WR.** 1977. Legionnaires' disease: isolation of a bacterium and demonstration of its role in other respiratory disease. N Engl J Med **297:**1197–1203.
177. **McMurray DN.** 1994. Guinea pig model of tuberculosis. In: Bloom BR, editor. Tuberculosis: pathogenesis, protection, and control. Washington (DC): American Society for Microbiology.
178. **McMurray DN.** 2001. Disease model: pulmonary tuberculosis. Trends Mol Med **7:**135–137.
179. **McMurray DN.** 2007. Personal communication.
180. **McMurray DN, Bartow RA.** 1992. Immunosuppression and alteration of resistance to pulmonary tuberculosis in guinea pigs by protein undernutrition. J Nutr **122:**738–743.
181. **McMurray DN, Bartow RA, Mintzer CL.** 1990. Protein malnutrition alters the distribution of Fc gamma R+ (T gamma) and Fc mu R+ (T mu) T lymphocytes in experimental pulmonary tuberculosis. Infect Immun **58:**563–565.
182. **McMurray DN, Collins FM, Dannenberg AM Jr, Smith DW.** 1996. Pathogenesis of experimental tuberculosis in animal models. Curr Top Microbiol Immunol **215:**157–179.
183. **McMurray DN, Mintzer CL, Tetzlaff CL, Carlomagno MA.** 1986. The influence of dietary protein on the protective effect of BCG in guinea pigs. Tubercle **67:**31–39.
184. **Menzies BE, Kourteva Y, Kaiser AB, Kernodle DS.** 2002. Inhibition of staphylococcal wound infection and potentiation of antibiotic prophylaxis by a recombinant fragment of the fibronectin-binding protein of *Staphylococcus aureus*. J Infect Dis **185:**937–943.
185. **Meurs H, Santing RE, Remie R, van der Mark TW, Westerhof FJ, Zuidhof AB, Bos IS, Zaagsma J.** 2006. A guinea pig model of acute and chronic asthma using permanently instrumented and unrestrained animals. Nat Protocols **1:**840–847.
186. **Miedzobrodzki J, Tadeusiewicz R.** 1987. Staphylococcal dermonecrotic reactions in guinea pigs. Int J Biomed Comput **21:**67–74.
187. **Ming X, Nichols M, Rothenburger S.** 2007. In vivo antibacterial efficacy of Monocryl plus antibacterial suture (poliglecaprone 25 with triclosan). Surg Infect (Larchmt) **8:**209–214.
188. **Miyamoto H, Yoshida S, Taniguchi H, Shuman HA.** 2003. Virulence conversion of *Legionella pneumophila* by conjugal transfer of chromosomal DNA. J Bacteriol **185:**6712–6718.
189. **Mizobuchi S, Minami J, Jin F, Matsushita O, Okabe A.** 1994. Comparison of the virulence of methicillin-resistant and methicillin-sensitive *Staphylococcus aureus*. Microbiol Immunol **38:**599–605.
190. **Moffat JF, Black WJ, Tompkins LS.** 1994. Further molecular characterization of the cloned *Legionella pneumophila* zinc metalloprotease. Infect Immun **62:**751–753.
191. **Moffat JF, Edelstein PH, Regula DP Jr, Cirillo JD, Tompkins LS.** 1994. Effects of an isogenic Zn-metalloprotease-deficient mutant of *Legionella pneumophila* in a guinea pig pneumonia model. Mol Microbiol **12:**693–705.
192. **Morris GK, Patton CM, Feeley JC, Johnson SE, Gorman G, Martin WT, Skaliy P, Mallison GF, Politi BD, Mackel DC.** 1979. Isolation of the Legionnaires' disease bacterium from environmental samples. Ann Intern Med **90:**664–666.

193. **Mount DT, Bigazzi PE, Barron AL.** 1972. Infection of genital tract and transmission of ocular infection to newborns by the agent of guinea pig inclusion conjunctivitis. Infect Immun **5:**921–926.
194. **Mount DT, Bigazzi PE, Barron AL.** 1973. Experimental genital infection of male guinea pigs with the agent of guinea pig inclusion conjunctivitis and transmission to females. Infect Immun **8:**925–930.
195. **Nagaoka I, Ishihara N, Yamashita T.** 1994. Characterization of the promoters of the guinea pig neutrophil cationic peptide 1 and 2 genes. FEBS Lett **356:**33–38.
196. **Nagaoka I, Nonoguchi A, Yamashita T.** 1993. Cloning and characterization of the guinea pig neutrophil cationic peptide 1 and 2 genes. DNA Seq **4:**123–128.
197. **Nagarajan UM, O'Connell C, Rank RG.** 2004. Molecular characterization of guinea pig (*Cavia porcellus*) CD8α and CD8β cDNA. Tissue Antigens **63:**184–189.
198. **Nakamura T, Sato H, Shimamura T, Koyama J.** 1988. The different roles of two distinct Fc gamma receptors on guinea pig macrophages in the phagocytosis of sensitized sheep erythrocytes. J Biochem **104:**383–387.
199. **Nakamura T, Tamoto K, Maeyama J, Sato H, Shimamura T, Koyama J.** 1987. Identification of an Fc receptor for IgG1 and IgG2 on guinea-pig polymorphonuclear leukocytes. Mol Immunol **24:**831–837.
200. **Neild AL, Roy CR.** 2003. *Legionella* reveal dendritic cell functions that facilitate selection of antigens for MHC class II presentation. Immunity **18:**813–823.
201. **Neild AL, Roy CR.** 2004. Immunity to vacuolar pathogens: what can we learn from *Legionella*? Cell Microbiol **6:**1011–1018.
202. **Nelson JL, Alexander JW, Gianotti L, Chalk CL, Pyles T.** 1996. High protein diets are associated with increased bacterial translocation in septic guinea pigs. Nutrition **12:**195–199.
203. **Nicholson A, Austen KF.** 1977. Isolation and characterization of guinea pig properidin. J Immunol **118:**103–108.
204. **Nikaido Y, Yoshida S, Goto Y, Mizuguchi Y, Kuroiwa A.** 1989. Macrophage-activating T cell factor(s) produced in an early phase of *Legionella pneumophila* infection in guinea pigs. Infect Immun **57:**3458–3465.
205. **Norris SJ.** 1993. Polypeptides of *Treponema pallidum*: progress toward understanding their structural, functional, and immunologic roles. *Treponema Pallidum* Polypeptide Research Group. Microbiol Rev **57:**750–779.
206. **O'Brien RJ.** 1993. The treatment of tuberculosis. In: Reichmann LB, Hershfield ES, editors. Tuberculosis: a comprehensive international approach. New York: Marcel Dekker. p 207–240
207. **Ohtani M, Kobayashi Y, Watanabe N.** 2004. Gene expression in the elicitation phase of guinea pig DTH and CHS reactions. Cytokine **25:**246–253.
208. **Onozaki K, Akagawa KS, Haga S, Miura K, Hashimoto T, Tokunaga T.** 1983. Role of lymphokines in regulation of macrophage differentiation. Cell Immunol **76:**129–136.
209. **Orenstein A, Klein D, Kopolovic J, Winkler E, Malik Z, Keller N, Nitzan Y.** 1997. The use of porphyrins for eradication of *Staphylococcus aureus* in burn wound infections. FEMS Immunol Med Microbiol **19:**307–314.
210. **Orme IM.** 2005. Current progress in tuberculosis vaccine development. Vaccine **23:**2105–2108.
211. **Orme IM.** 2005. Mouse and guinea pig models for testing new tuberculosis vaccines. Tuberculosis (Edinb) **85:**13–17.
212. **Orme IM.** 2005. Tuberculosis vaccines: current progress. Drugs **65:**2437–2444.
213. **Orme IM.** 2006. Preclinical testing of new vaccines for tuberculosis: a comprehensive review. Vaccine **24:**2–19.
214. **Orme IM, McMurray DN, Belisle JT.** 2001. Tuberculosis vaccine development: recent progress. Trends Microbiol **9:**115–118.
215. **O'Rourke E, Schweon S.** 2007. Syphillis. Still a public health danger. RN **70:**26–31, quiz 32.
216. **Pal PG, Horwitz MA.** 1992. Immunization with extracellular proteins of Mycobacterium tuberculosis induces cell-mediated immune responses and substantial protective immunity in a guinea pig model of pulmonary tuberculosis. Infect Immun **60:**4781–4792.
217. **Pasley JN, Rank RG, Hough AJ Jr, Cohen C, Barron AL.** 1985. Absence of progesterone effects on chlamydial genital infection in female guinea pigs. Sex Transm Dis **12:**155–158.
218. **Pasley JN, Rank RG, Hough AJ Jr, Cohen C, Barron AL.** 1985. Effects of various doses of estradiol on chlamydial genital infection in ovariectomized guinea pigs. Sex Transm Dis **12:**8–13.
219. **Patterson TL, Rank RG.** 1996. Immunity to reinfection and immunization of male guinea pigs against urethral infection with the agent of guinea pig inclusion conjunctivitis. Sex Transm Dis **23:**145–150.
220. **Pavia CS.** 1986. Enhanced primary resistance to *Treponema pallidum* infection and increased susceptibility to toxoplasmosis in T-cell-depleted guinea pigs. Infect Immun **53:**305–311.
221. **Pavia CS.** 1986. Transfer of resistance to syphilitic infection from maternal to newborn guinea pigs. Infect Immun **51:**365–368.
222. **Pavia CS, Niederbuhl CJ.** 1985. Acquired resistance and expression of a protective humoral immune response in guinea pigs infected with *Treponema pallidum* Nichols. Infect Immun **50:**66–72.
223. **Pavia CS, Niederbuhl CJ.** 1985. Adoptive transfer of antisyphilis immunity with lymphocytes from *Treponema pallidum*-infected guinea pigs. J Immunol **135:**2829–2834.
224. **Pavia CS, Niederbuhl CJ.** 1985. Experimental infection of inbred guinea pigs with *Treponema pallidum*: development of lesions and formation of antibodies. Genitourin Med **61:**75–81.
225. **Pavia CS, Niederbuhl CJ, Saunders J.** 1985. Antibody-mediated protection of guinea pigs against infection with *Treponema pallidum*. Immunology **56:**195–202.
226. **Peck MD, Alexander JW.** 1991. Survival in septic guinea pigs is influenced by vitamin E, but not by vitamin C in enteral diets. JPEN J Parenter Enteral Nutr **15:**433–436.
227. **Pierce CS, Wicher K, Nakeeb S.** 1983. Experimental syphilis: guinea pig model. Br J Vener Dis **59:**157–168.
228. **Platt J, Bucknall RA.** 1984. An experimental evaluation of antiseptic wound irrigation. J Hosp Infect **5:**181–188.
229. **Porcelli SA, Modlin RL.** 1999. The CD1 system: antigen-presenting molecules for T cell recognition of lipids and glycolipids. Annu Rev Immunol **17:**297–329.
230. **Pre-Ensembl.** [Internet]. August 2007. Cambridge (UK):WTSI/EBI; c2008 [cited 2007 August]. Available from: http://pre.ensembl.org/Cavia_porcellus/index.html.
231. **Quinn J, Maw J, Ramotar K, Wenckebach G, Wells G.** 1997. Octylcyanoacrylate tissue adhesive versus suture wound repair in a contaminated wound model. Surgery **122:**69–72.
232. **Rajagopalan-Levasseur P, Lecointe D, Bertrand G, Fay M, Gougerot-Pocidalo MA.** 1996. Differential nitric oxide (NO) production by macrophages from mice and guinea pigs infected with virulent and avirulent *Legionella pneumophila* serogroup 1. Clin Exp Immunol **104:**48–53.
233. **Raju B, Hoshino Y, Kuwabara K, Belitskaya I, Prabhakar S, Canova A, Gold JA, Condos R, Pine RI, Brown S, Rom WN, Weiden MD.** 2004. Aerosolized γ interferon (IFNγ) induces expression of the genes encoding the IFNγ-inducible 10-kDa protein but not inducible nitric oxide synthase in the lung during tuberculosis. Infect Immun **72:**1275–1283.
234. **Rank RG.** 1999. Models of immunity. In: Stephens RS, editor. Chlamydia: intracellular biology, pathogenesis, and immunity. Washington (DC): American Society for Microbiology. p. 239–295
235. **Rank RG, Barron AL.** 1983. Effect of antithymocyte serum on the course of chlamydial genital infection in female guinea pigs. Infect Immun **41:**876–879.
236. **Rank RG, Barron AL.** 1983. Humoral immune response in acquired immunity to chlamydial genital infection of female guinea pigs. Infect Immun **39:**463–465.
237. **Rank RG, Barron AL.** 1987. Specific effect of estradiol on the genital mucosal antibody response in chlamydial ocular and genital infections. Infect Immun **55:**2317–2319.

238. **Rank RG, Batteiger BE.** 1989. Protective role of serum antibody in immunity to chlamydial genital infection. Infect Immun **57:**299–301.
239. **Rank RG, Batteiger BE, Soderberg LS.** 1988. Susceptibility to reinfection after a primary chlamydial genital infection. Infect Immun **56:**2243–2249.
240. **Rank RG, Batteiger BE, Soderberg LS.** 1990. Immunization against chlamydial genital infection in guinea pigs with UV-inactivated and viable chlamydiae administered by different routes. Infect Immun **58:**2599–2605.
241. **Rank RG, Bowlin AK, Kelly KA.** 2000. Characterization of lymphocyte response in the female genital tract during ascending chlamydial genital infection in the guinea pig model. Infect Immun **68:**5293–5298.
242. **Rank RG, Bowlin AK, Reed RL, Darville T.** 2003. Characterization of chlamydial genital infection resulting from sexual transmission from male to female guinea pigs and determination of infectious dose. Infect Immun **71:**6148–6154.
243. **Rank RG, Sanders MM, Patton DL.** 1995. Increased incidence of oviduct pathology in the guinea pig after repeat vaginal inoculation with the chlamydial agent of guinea pig inclusion conjunctivitis. Sex Transm Dis **22:**48–54.
244. **Rank RG, White HJ, Barron AL.** 1979. Humoral immunity in the resolution of genital infection in female guinea pigs infected with the agent of guinea pig inclusion conjunctivitis. Infect Immun **26:**573–579.
245. **Rank RG, White HJ, Hough AJ Jr, Pasley JN, Barron AL.** 1982. Effect of estradiol on chlamydial genital infection of female guinea pigs. Infect Immun **38:**699–705.
246. **Rank RG, White HJ, Soloff BL, Barron AL.** 1981. Cystitis associated with chlamydial infection of the genital tract in male guinea pigs. Sex Transm Dis **8:**203–210.
247. **Robinson AJ, Ridgway GL.** 1996. Modern diagnosis and management of genital *Chlamydia trachomatis* infection. Br J Hosp Med **55:**388–393.
248. **Roche PW, Triccas JA, Winter N.** 1995. BCG vaccination against tuberculosis: past disappointments and future hopes. Trends Microbiol **3:**397–401.
249. **Sato M, Nakamura T, Koyama J.** 1987. Different abilities of two distinct Fcγ receptors on guinea pig polymorphonuclear leukocytes to trigger the arachidonic acid metabolic cascade. FEBS Lett **224:**29–32.
250. **Sato M, Nakamura T, Koyama J.** 1988. Two distinct Fcγ Rs on guinea pig polymorphonuclear leukocytes differ from each other in their eliciting activities for O_2 generation. Mol Immunol **25:**205–211.
251. **Scarozza AM, Ramsingh AI, Wicher V, Wicher K.** 1998. Spontaneous cytokine gene expression in normal guinea pig blood and tissues. Cytokine **10:**851–859.
252. **Schaad HJ, Chuard C, Vaudaux P, Waldvogel FA, Lew DP.** 1994. Teicoplanin alone or combined with rifampin compared with vancomycin for prophylaxis and treatment of experimental foreign body infection by methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **38:**1703–1710.
253. **Schachter J, Cles LD, Ray RM, Hesse FE.** 1983. Is there immunity to chlamydial infections of the human genital tract? Sex Transm Dis **10:**123–125.
254. **Schrod L, Schaefer H, Burger R.** 1986. Characterization of a T lymphocyte membrane protein involved in T cell function: its contribution to T cell recognition or cellular interaction. Immunology **57:**533–538.
255. **Senn MM, Giachino P, Homerova D, Steinhuber A, Strassner J, Kormanec J, Fluckiger U, Berger-Bachi B, Bischoff M.** 2005. Molecular analysis and organization of the σB operon in *Staphylococcus aureus*. J Bacteriol **187:**8006–8019.
256. **Seya T, Okada M, Hazeki K, Nagasawa S.** 1991. Regulatory system of guinea pig complement C3b: tests for compatibility of guinea pig factors H and I with human factors. Mol Immunol **28:**375–382.
257. **Sheffield CW, Sessler DI, Hunt TK, Scheuenstuhl H.** 1994. Mild hypothermia during halothane-induced anesthesia decreases resistance to *Staphylococcus aureus* dermal infection in guinea pigs. Wound Repair Regen **2:**48–56.
258. **Shimokawa Y, Harita S, Hayashi H.** 1984. Lymphocyte chemotaxis in inflammation. VII. Isolation and purification of chemotactic factors for T lymphocytes from PPD-induced delayed hypersensitivity skin reaction site in the guinea pig. Immunology **51:**275–285.
259. **Shimokawa Y, Harita S, Higuchi Y, Hayashi H.** 1982. Lymphocyte chemotaxis in inflammation. III. Demonstration of lymphocyte chemotactic activity in extract from PPD-induced delayed hypersensitivity skin reaction site in the guinea pig. Br J Exp Pathol **63:**355–361.
260. **Shimokawa Y, Harita S, Higuchi Y, Hayashi H.** 1982. Lymphocyte chemotaxis in inflammation. IV. Isolation of lymphocyte chemotactic factors from PPD-induced delayed hypersensitivity skin reaction site in the guinea pig, with special reference to a factor chemotactic for B cells. Br J Exp Pathol **63:**362–368.
261. **Shimokawa Y, Harita S, Mibu Y, Hayashi H.** 1984. Lymphocyte chemotaxis in inflammation. VIII. Demonstration of lymphocyte chemotactic lymphokines in PPD-induced delayed hypersensitivity skin reaction site in the guinea pig. Immunology **51:**287–294.
262. **Shiratori I, Matsumoto M, Tsuji S, Nomura M, Toyoshima K, Seya T.** 2001. Molecular cloning and functional characterization of guinea pig IL12. Int Immunol **13:**1129–1139.
263. **Siddiqui SM, Orme IM, Saxena RK.** 2000. Efficacy of culture filtrate protein preparations from Indian isolates of *M. tuberculosis* to activate T cells derived from healthy donors. Int J Tuberc Lung Dis **4:**980–987.
264. **Singer L, Colten HR, Wetsel RA.** 1994. Complement C3 deficiency: human, animal, and experimental models. Pathobiology **62:**14–28.
265. **Skeiky YA, Sadoff JC.** 2006. Advances in tuberculosis vaccine strategies. Nat Rev Microbiol **4:**469–476.
266. **Skwor TA, Cho H, Cassidy C, Yoshimura T, McMurray DN.** 2004. Recombinant guinea pig CCL5 (RANTES) differentially modulates cytokine production in alveolar and peritoneal macrophages. J Leukoc Biol **76:**1229–1239.
267. **Skwor TA, Sedberry Allen S, Mackie JT, Russell K, Berghman LR, McMurray DN.** 2006. BCG vaccination of guinea pigs modulates *Mycobacterium tuberculosis*-induced CCL5 (RANTES) production in vitro and in vivo. Tuberculosis (Edinb) **86:**419–429.
268. **Smith DW, McMurray DN, Wiegeshaus EH, Grover AA, Harding GE.** 1970. Host–parasite relationships in experimental airborne tuberculosis. IV. Early events in the course of infection in vaccinated and nonvaccinated guinea pigs. Am Rev Respir Dis **102:**937–949.
269. **Smith S, Gantt N, Rowe MI, Lloyd DA.** 1989. Dura versus Gore-Tex as an abdominal wall prosthesis in an open and closed infected model. J Pediatr Surg **24:**519–521.
270. **Soloff BL, Rank RG, Barron AL.** 1985. Electron microscopic observations concerning the in vivo uptake and release of the agent of guinea pig inclusion conjunctivitis (*Chlamydia psittaci*) in guinea pig exocervix. J Comp Pathol **95:**335–344.
271. **Storch ML, Rothenburger SJ, Jacinto G.** 2004. Experimental efficacy study of coated Vicryl plus antibacterial suture in guinea pigs challenged with *Staphylococcus aureus*. Surg Infect (Larchmt) **5:**281–288.
272. **Stratford AF, Zoutman DE, Davidson JS.** 2002. Effect of lidocaine and epinephrine on *Staphylococcus aureus* in a guinea pig model of surgical wound infection. Plast Reconstr Surg **110:**1275–1279.
273. **Suarez S, O'Hara P, Kazantseva M, Newcomer CE, Hopfer R, McMurray DN, Hickey AJ.** 2001. Airways delivery of rifampicin microparticles for the treatment of tuberculosis. J Antimicrob Chemother **48:**431–434.
274. **Suarez S, O'Hara P, Kazantseva M, Newcomer CE, Hopfer R, McMurray DN, Hickey AJ.** 2001. Respirable PLGA microspheres containing rifampicin for the treatment of tuberculosis: screening in an infectious disease model. Pharm Res **18:**1315–1319.
275. **Takahashi M, Jeevan A, Sawant K, McMurray DN, Yoshimura T.** 2007. Cloning and characterization of guinea pig *CXCR1*. Mol Immunol **44:**878–888.

276. **Takizawa M, Chiba J, Haga S, Asano T, Yamamoto N, Honda M.** 2004. The normalization of guinea pig leukocyte fractions and lymphocyte subsets in blood and lymphoid tissues using a flow cytometric procedure. Exp Anim **53:**321–329.
277. **Takizawa M, Chiba J, Haga S, Asano T, Yamazaki T, Yamamoto N, Honda M.** 2006. Novel two-parameter flow cytometry (MIL4/SSC followed by MIL4/CT7) allows for identification of five fractions of guinea pig leukocytes in peripheral blood and lymphoid organs. J Immunol Methods **311:**47–56.
278. **Tateda K, Matsumoto T, Ishii Y, Furuya N, Ohno A, Miyazaki S, Yamaguchi K.** 1998. Serum cytokines in patients with *Legionella pneumonia*: relative predominance of Th1-type cytokines. Clin Diagn Lab Immunol **5:**401–403.
279. **Tominaga M, Sakata A, Ohmura T, Yamashita T, Koyama J, Onoue K.** 1990. The structure and expression of the guinea pig Fc receptor for IgG1 and IgG2 (Fcγ1/γ2R). Biochem Biophys Res Commun **168:**683–689.
280. **Tree JA, Elmore MJ, Javed S, Williams A, Marsh PD.** 2006. Development of a guinea pig immune response-related microarray and its use to define the host response following *Mycobacterium bovis* BCG vaccination. Infect Immun **74:**1436–1441.
281. **Turner OC, Basaraba RJ, Orme IM.** 2003. Immunopathogenesis of pulmonary granulomas in the guinea pig after infection with *Mycobacterium tuberculosis*. Infect Immun **71:**864–871.
282. **Valet G, Jenssen HL, Krefft M, Ruhenstroth-Bauer G.** 1981. Flow-cytometric measurements of the transmembrane potential, the surface charge density and the phagocytic activity of Guinea pig macrophages after incubation with lymphokines. Blut **42:**379–382.
283. **van Voorhis WC, Barrett LK, Nasio JM, Plummer FA, Lukehart SA.** 1996. Lesions of primary and secondary syphilis contain activated cytolytic T cells. Infect Immun **64:**1048–1050.
284. **Vaudaux P, Francois P, Bisognano C, Schrenzel J, Lew DP.** 2002. Comparison of levofloxacin, alatrofloxacin, and vancomycin for prophylaxis and treatment of experimental foreign-body-associated infection by methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **46:**1503–1509.
285. **Vaudaux P, Suzuki R, Waldvogel FA, Morgenthaler JJ, Nydegger UE.** 1984. Foreign body infection: role of fibronectin as a ligand for the adherence of *Staphylococcus aureus*. J Infect Dis **150:**546–553.
286. **Vogel FR, Klein TW, Specter SC, Hitchings M, Friedman H.** 1981. Detection of antibodies to *Legionella pneumophila* in immune guinea pig serum by solid-phase immunofluorescence. J Clin Microbiol **13:**726–729.
287. **von Behring E.** 1890. Untersuchungen uber das Zustanddekommen der Diphtherie-Immunitat bei Theiren. Dtsch Med Wochenschr **16:**1145.
288. **Wagner C, Khan AS, Kamphausen T, Schmausser B, Unal C, Lorenz U, Fischer G, Hacker J, Steinert M.** 2007. Collagen binding protein Mip enables *Legionella pneumophila* to transmigrate through a barrier of NCI-H292 lung epithelial cells and extracellular matrix. Cell Microbiol **9:**450–462.
289. **Ward ME.** 1999. Mechanisms of *Chlamydia*-induced disease. In: Stephens RS, editor. *Chlamydia*: intracellular biology, pathogenesis, and immunity. Washington (DC): American Society for Microbiology. p. 171–210
290. **Washington AE, Gove S, Schachter J, Sweet RL.** 1985. Oral contraceptives, *Chlamydia trachomatis* infection, and pelvic inflammatory disease. A word of caution about protection. J Am Med Assoc **253:**2246–2250.
291. **Weeratna R, Stamler DA, Edelstein PH, Ripley M, Marrie T, Hoskin D, Hoffman PS.** 1994. Human and guinea pig immune responses to *Legionella pneumophila* protein antigens OmpS and Hsp60. Infect Immun **62:**3454–3462.
292. **White HJ, Rank RG, Soloff BL, Barron AL.** 1979. Experimental chlamydial salpingitis in immunosuppressed guinea pigs infected in the genital tract with the agent of guinea pig inclusion conjunctivitis. Infect Immun **26:**728–735.
293. **Wicher K, Abbruscato F, Wicher V, Baughn R, Noordhoek GT.** 1996. Target organs of infection in guinea pigs with acquired congenital syphilis. Infect Immun **64:**3174–3179.
294. **Wicher K, Baughn RE, Wicher V, Nakeeb S.** 1992. Experimental congenital syphilis: guinea pig model. Infect Immun **60:**271–277.
295. **Wicher K, Jakubowski A.** 1964. Effect of cortisone on the course of experimental syphilis in the guinea-pig. I. Effect of previously administered cortisone on guinea pigs infected with *Treponema pallidum* intradermally, intratesticularly, and intravenously. Br J Vener Dis **40:**213–216.
296. **Wicher K, Jakubowski A, Wicher V.** 1987. Humoral response in *Treponema pallidum*-infected guinea pigs: I. Antibody specificity. Clin Exp Immunol **69:**263–270.
297. **Wicher K, Miller JN, Urquhart AW, Wicher V.** 1989. *Treponema pallidum*-immobilizing antibodies in guinea pig experimental syphilis. Infect Immun **57:**2900–2902.
298. **Wicher K, Schouls LM, Wicher V, Van Embden JD, Nakeeb SS.** 1991. Immunization of guinea pigs with recombinant TmpB antigen induces protection against challenge infection with *Treponema pallidum* Nichols. Infect Immun **59:**4343–4348.
299. **Wicher K, van Embden JD, Schouls LM, Zabek J, Jakubowski A, Wicher V.** 1989. Immunogenicity of three recombinant *Treponema pallidum* antigens examined in guinea pigs. Int Arch Allergy Appl Immunol **89:**128–135.
300. **Wicher K, Wicher V.** 1989. Experimental syphilis in guinea pig. Crit Rev Microbiol **16:**181–234.
301. **Wicher K, Wicher V, Abbruscato F, Baughn RE.** 2000. *Treponema pallidum* subsp. pertenue displays pathogenic properties different from those of *T. pallidum* subsp. pallidum. Infect Immun **68:**3219–3225.
302. **Wicher K, Wicher V, Gruhn RF.** 1985. Differences in susceptibility to infection with *Treponema pallidum* (Nichols) between five strains of guinea pig. Genitourin Med **61:**21–26.
303. **Wicher K, Wicher V, Jakubowski A, Bartholomew W, Nakeeb S.** 1988. Effect of irradiation and depletion of C3-complement component on the course of *Treponema pallidum* infection in a resistant guinea pig strain. Int Arch Allergy Appl Immunol **86:**76–81.
304. **Wicher K, Wicher V, Jakubowski A, Gruhn R.** 1988. Factors affecting the clinical course of *Treponema pallidum* infection in guinea pigs. Int Arch Allergy Appl Immunol **85:**252–256.
305. **Wicher K, Wicher V, Wang MC.** 1976. Cellular and humoral immune response to guinea pig infected with *Treponema pallidum*. Int Arch Allergy Appl Immunol **51:**284–297.
306. **Wicher K, Zabek J, Wicher V.** 1992. Effect of passive immunization with purified specific or cross-reacting immunoglobulin G antibodies against *Treponema pallidum* on the course of infection in guinea pigs. Infect Immun **60:**3217–3223.
307. **Wicher V, Scarozza AM, Ramsingh AI, Wicher K.** 1998. Cytokine gene expression in skin of susceptible guinea pigs infected with *Treponema pallidum*. Immunology **95:**242–247.
308. **Wicher V, Wicher K, Abbruscato F, Auger I, Rudofsky U.** 1999. The time-dependent clearance of virulent *Treponema pallidum* in susceptible and resistant strains of guinea pigs is significantly different. Clin Immunol **91:**77–83.
309. **Wicher V, Wicher K, Jakubowski A, Nakeeb SM.** 1987. Adoptive transfer of immunity to *Treponema pallidum* Nichols infection in inbred strain 2 and C4D guinea pigs. Infect Immun **55:**2502–2508.
310. **Wicher V, Zabek J, Wicher K.** 1989. Kinetics of pathogen-specific humoral response in *Treponema pallidum*-infected young and old inbred strain 2 guinea pigs. Clin Exp Immunol **77:**144–150.
311. **Wicher V, Zabek J, Wicher K.** 1991. Pathogen-specific humoral response in *Treponema pallidum*-infected humans, rabbits, and guinea pigs. J Infect Dis **163:**830–836.
312. **Widen R, Lee I, Klein T, Friedman H.** 1983. Blastogenic responsiveness of spleen cells from guinea pigs sensitized to *Legionella pneumophila* antigens. Proc Soc Exp Biol Med **173:**547–552.
313. **Williams A, Lever MS.** 1995. Characterisation of *Legionella pneumophila* antigen in urine of guinea pigs and humans with Legionnaires' disease. J Infect **30:**13–16.

314. **Winn WC Jr, Chandler FW.** 1982. Role of virulence factors in *Legionella* infections. Arch Pathol Lab Med **106:**105–107.
315. **Winn WC Jr, Davis GS, Gump DW, Craighead JE, Beaty HN.** 1982. Legionnaires' pneumonia after intratracheal inoculation of guinea pigs and rats. Lab Invest **47:**568–578.
316. **Wolz C, Goerke C, Landmann R, Zimmerli W, Fluckiger U.** 2002. Transcription of clumping factor A in attached and unattached *Staphylococcus aureus* in vitro and during device-related infection. Infect Immun **70:**2758–2762.
317. **Wong KH, Schalla WO, Arko RJ, Bullard JC, Feeley JC.** 1979. Immunochemical, serologic, and immunologic properties of major antigens isolated from the Legionnaires' disease bacterium. Observations bearing on the feasibility of a vaccine. Ann Intern Med **90:**634–638.
318. **Xiong X, Morita CT, Bukowski JF, Brenner MB, Dascher CC.** 2004. Identification of guinea pig γδ T cells and characterization during pulmonary tuberculosis. Vet Immunol Immunopathol **102:**33–44.
319. **Yamada H, Udagawa T, Mizuno S, Hiramatsu K, Sugawara I.** 2005. Newly designed primer sets available for evaluating various cytokines and iNOS mRNA expression in guinea pig lung tissues by RT-PCR. Exp Anim **54:**163–172.
320. **Yamamoto C, Yoshida S, Taniguchi H, Qin MH, Miyamoto H, Mizuguchi Y.** 1993. Lipopolysaccharide and granulocyte colony-stimulating factor delay neutrophil apoptosis and ingestion by guinea pig macrophages. Infect Immun **61:**1972–1979.
321. **Yamamoto T, Jeevan A, Ohishi K, Nojima Y, Umemori K, Yamamoto S, McMurray DN.** 2002. A new assay system for guinea pig interferon biological activity. J Interferon Cytokine Res **22:**793–797.
322. **Yamamoto Y, Klein TW, Newton CA, Widen R, Friedman H.** 1987. Differential growth of *Legionella pneumophila* in guinea pig versus mouse macrophage cultures. Infect Immun **55:**1369–1374.
323. **Yang D, Nakada-Tsukui K, Ohtani M, Goto R, Yoshimura T, Kobayashi Y, Watanabe N.** 2001. Identification and cloning of genes associated with the guinea pig skin delayed-type hypersensitivity reaction. J Biochem **129:**561–568.
324. **Yomogida S, Nagaoka I, Saito K, Yamashita T.** 1996. Evaluation of the effects of defensins on neutrophil functions. Inflamm Res **45:**62–67.
325. **Yomogida S, Nagaoka I, Yamashita T.** 1996. Purification of the 11- and 5-kDa antibacterial polypeptides from guinea pig neutrophils. Arch Biochem Biophys **328:**219–226.
326. **Yomogida S, Nagaoka I, Yamashita T.** 1997. Comparative studies on the extracellular release and biological activity of guinea pig neutrophil cationic antibacterial polypeptide of 11 kDa (CAP11) and defensins. Comp Biochem Physiol B Biochem Mol Biol **116:**99–107.
327. **Yoshida S, Mizuguchi Y.** 1986. Multiplication of *Legionella pneumophila* Philadelphia 1 in cultured peritoneal macrophages and its correlation to susceptibility of animals. Can J Microbiol **32:**438–442.
328. **Yoshimura T, Johnson DG.** 1993. cDNA cloning and expression of guinea pig neutrophil attractant protein 1 (NAP1). NAP1 is highly conserved in guinea pig. J Immunol **151:**6225–6236.
329. **Zhang X, McMurray DN.** 1998. Suppression of lymphoproliferation by alveolar macrophages in the guinea pig. Tuber Lung Dis **79:**119–126.
330. **Zhao J, Wicher V, Burger R, Schafer H, Wicher K.** 1992. Strain- and age-associated differences in lymphocyte phenotypes and immune responsiveness in C4-deficient and Albany strains of guinea pigs. Immunology **77:**165–170.
331. **Zimmerli W**. 1993. Experimental models in the investigation of device-related infections. J Antimicrob Chemother **31 Suppl D:**97–102.
332. **Zimmerli W, Lew PD, Waldvogel FA.** 1984. Pathogenesis of foreign body infection. Evidence for a local granulocyte defect. J Clin Invest **73:**1191–1200.
333. **Zimmerli W, Waldvogel FA, Vaudaux P, Nydegger UE.** 1982. Pathogenesis of foreign body infection: description and characteristics of an animal model. J Infect Dis **146:**487–497.
334. **Zimmerli W, Zak O, Vosbeck K.** 1985. Experimental hematogenous infection of subcutaneously implanted foreign bodies. Scand J Infect Dis **17:**303–310.