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The Contribution of Non-human Primate Models to the Development of Human Vaccines

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Abstract

The nonhuman primates (NHPs) model in biomedical research has contributed to the study of human infectious, autoimmune, oncogenic, and neurological diseases. This review focuses on the importance of NHP models in vaccine development for tuberculosis, pertussis, Dengue, group A streptococcus (*Streptococcus pyogenes*) infection, HIV infection, and certain diseases in the

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elderly (influenza, for example). From understanding disease pathogenesis and mechanisms of protection, to assessing vaccine safety and efficacy, we discuss selected cases where the importance of the use of NHP models is highlighted.

Introduction

Innovation and development of treatment and preventative measures against infectious diseases has been largely based on the study of host-pathogen interactions through the use of animal models. Mice have been the primary model used due to ease in handling, low cost, and availability of a diverse range of genetically modified strains that can be applied to examine specific disease processes. However, the non-susceptibility of mice to the majority of human-adapted pathogens represents a major hurdle in establishing infection models that mimic human disease. Differences in anatomy and immune responses between the human and mouse species, and the inbred nature of many mouse lines, represent some of the additional disadvantages of modeling human disease in rodents. It is important not to minimize the contribution of murine models in infectious disease research, which have allowed dissection of the varied immune responses to different pathogens and have provided the foundation for developing treatments and vaccines in a rapid and accessible manner. However, in order to translate the discovery of these treatments and vaccines into potential clinical outcomes, it is also important to make use of higher animal models such as non-human primates (NHPs). This review focuses on the use of NHP models for the development of vaccines, not only by providing reliable models for immunogenicity and safety testing, but also by contributing to the understanding of pathogenesis and potential correlates of protection. NHPs have been used for vaccine testing for a number of viral, bacterial, and parasitic diseases, and here we focus on specific cases where we consider that NHPs have or will play a key role in vaccine development.

Tuberculosis

Tuberculosis (TB) is one of the greatest causes of human mortality. According to the World Health Organization (WHO), in 2013 over 1.5 million people died from TB and 9 million people suffered from the disease. It has been estimated that 1/3 of the world population is latently infected with *Mycobacterium tuberculosis*, which will emerge as active TB in approximately 10% of infected individuals. The only licensed TB vaccine, *Mycobacterium bovis* bacille Calmette-Guerin (BCG), is used in countries with high prevalence of TB due to the protective efficacy offered against extra-pulmonary TB in infants, namely childhood tuberculosis meningitis. Unfortunately BCG has variable levels of efficacy against pulmonary TB (Trunz *et al.*, 2006). A vaccine that not only provides protection against TB meningitis but also against pulmonary disease is one of the research priorities of the WHO (Stop TB Partnership, 2011) in order to reduce the burden of TB worldwide.

Several animal models have been used to study TB pathogenesis. In particular the mouse and guinea pig models have been used extensively and have contributed a great deal to the understanding of disease pathogenesis, drug development, and vaccine candidate identification. Since it generates human-like disease following infection via the respiratory route, the NHP model has gained greater attention in recent years (McMurray, 2000). The

NHP model allows researchers to monitor correlates of infection and apply advanced imaging techniques to assess pulmonary lesions (Sharpe *et al.*, 2009). Walsh and collaborators developed an intratracheal infection model in cynomolgus macaques (*Macaca fasicularis*) that showed correlation between disease severity and the amount of challenge dose delivered. This allowed assessment of either acute disease or chronic progressive granulomatous disease similar to human TB (Walsh *et al.*, 1996). Importantly, in addition to demonstrating a spectrum of granulomatous disease closely resembling that of humans, cynomolgus macaques remain the best model of latent infection (Lin *et al.*, 2009). Finally, the macaque can also be utilized in studies of simian immunodeficiency virus and implications of co-infection for anti-TB vaccination (Shen *et al.*, 2002).

One of the strategies to improve vaccine efficacy against pulmonary TB is to develop a booster vaccine that can improve BCG immunity. Antigens from *M. tuberculosis* that were recognized by T cells from patients with latent TB were identified and combined in a poly-protein vaccine candidate designated Mtb72F (Brandt *et al.*, 2004; Dillon *et al.*, 1999; Irwin *et al.*, 2005; Tsenova *et al.*, 2006). The Mtb72F candidate formulated in AS02A adjuvant was evaluated using the cynomolgus model as a potential boost for BCG (Reed *et al.*, 2009). NHPs were monitored for survival, histological, and clinical parameters, and the bacterial burden quantified. Animals that received a BCG prime immunization followed by three Mtb72F/AS02A boosts had higher levels of protection than NHPs that received BCG only. Characterization of the cellular immune response in Mtb72F/AS02A-boosted NHPs showed proliferation of IFN-γ, IL-2, and TNF-α producing cells which are generally associated with protection against TB (Nunes-Alves *et al.*, 2014). This data provided a solid basis to forward this prime/boost strategy into clinical trials where a new version of the Mtb72F antigen, named M72, was shown to be safe and immunogenic in both healthy (Leroux-Roels *et al.*, 2013; 2010; Spertini *et al.*, 2013) and HIV-infected human adults (Thacher *et al.*, 2014).

Another booster vaccine developed by Aagaard and colleagues consists of a combination of three antigens. Two antigens (Ag85B and ESAT-6) are expressed in the early stages of infection and the third antigen (Rv2660c) is upregulated during latent infection (Aagaard *et al.*, 2011). The multistage vaccine H56 adjuvanted with IC31 (Intercell) was evaluated as a booster vaccine for BCG in the cynomolgus model against a low and a high TB challenge dose (Lin *et al.*, 2012). BCG immunized NHPs boosted with H56/IC31 showed reduced rates of clinical disease compared to NHPs immunized with BCG only. Moreover, NHPs boosted with H56/IC31 were protected against reactivation of latent TB (Lin *et al.*, 2012; 2010), a feature that would greatly increase the effectiveness of this vaccine candidate for reducing the burden of TB (Kaufmann, 2011).

Recently, researchers have utilized the rhesus macaque (*Macaca mulatta*) model to investigate aerosolized vaccines (Darrah *et al.*, 2014). Although the vaccine trialed here, AERAS-402, failed to fully protect monkeys from *M. tuberculosis* challenge, strong antigen-specific, cell-mediated responses were generated in the lung, the site of vaccination. NHPs will play a key role in the evaluation of the efficacy of novel TB vaccine candidates and vaccination strategies in the future, as well as identifying potential correlates of protection that can be monitored during subsequent clinical trials (Dutta *et al.*, 2014; Wareham *et al.*, 2014).

Pertussis

According to a report from the Centers for Disease Control and Prevention (CDC), in 2012 in the U.S. there was a peak of whooping cough cases, the highest reported in 50 years (CDC, 2012). Although the number of total cases decreased in 2013, during the first half of 2014 the reported cases were 30% higher compared with the same time period in the previous year (CDC, 2014). This resurgence in whooping cough has been observed despite vaccine coverage in the U.S. of 95% for the acellular pertussis vaccine (aP) in children (CDC, 2013). Hypotheses to explain the increase in pertussis prevalence include variation in *Bordetella pertussis* antigens included in the aP vaccine (Thalen *et al.*, 2008), and the lower potency of the aP vaccine introduced in the 1990's compared to the DTP whole cell vaccine (wP) used previously (Cherry, 2012; He and Mertsola, 2008). A major hurdle to examining these hypotheses is the limited understanding of disease pathogenesis and correlates of protection. These limitations emphasize the need for reliable animal models that resemble human disease to allow investigation of the mechanisms of protection provided by vaccination (van der Ark *et al.*, 2012).

Warfel and collaborators developed a non-human primate model for pertussis infection and characterized the mucosal immune response following infection. Baboons (*Papio anubis*) infected with *B. pertussis*, developed respiratory colonization and leukocytosis, and the model was able to reproduce cough and airborne transmission (Warfel *et al.*, 2012a; 2012b). Furthermore, by using the baboon model for pertussis infection, Warfel and colleagues were able to evaluate the efficacy of aP and wP vaccines using a challenge model that resembles disease in humans. The study found that aP vaccines were able to protect baboons from severe disease; however, they did not prevent bacterial colonization. Animals vaccinated with aP were able to transmit the disease to naive animals. On the other hand, wP vaccinated animals had initial levels of colonization similar to aP vaccinated animals, but were able to clear the infection better than aP vaccinated animals (Warfel *et al.*, 2014). Antibody levels raised by both vaccines were similar; however, significant differences were found in the T helper (Th) response that both vaccines elicited. The aP vaccine induced a Th2 or mixed Th1/Th2 response, whereas the wP vaccine induced a Th17/Th1 response, weaker but similar to that induced by natural infection (Warfel and Merkel, 2013). The design of a new vaccine or improvement of the current aP vaccine should be strongly supported by the use of the baboon model, placing emphasis on improving Th17/Th1 response and stimulating solid immunological memory (Ausiello and Cassone, 2014); both parameters that can be measured and characterized in this model. In addition, this model could play a major role in the study and monitoring of vaccine efficacy against new circulating vaccine-adapted *B. pertussis* strains (van der Ark *et al.*, 2012).

Dengue

Dengue fever is a mosquito-borne viral disease found mainly in tropical and subtropical regions around the world, and represents one of the largest public health burdens globally. The incidence of dengue has increased dramatically in the past few decades with more than 400 million infections and 100 million symptomatic cases now occurring annually. As many as 3.6 billion people are at risk of infection in areas where the major mosquito vector, *Aedes*

aegypti, is found (Bhatt *et al.*, 2013). Treatment is limited to palliative care, as there is no effective antiviral drug or vaccine clinically available. There are 4 different virus serotypes that cause dengue disease (DENV-1, DENV-2, DENV-3, and DENV-4). Infection and recovery from one specific serotype provides long-lasting protection against that particular serotype, whereas cross-protection against other serotypes is partial and temporary. Subsequent heterotypic infections are thought to increase the risk of developing severe complications of dengue infection, dengue hemorrhagic fever, and dengue shock syndrome (DHF and DSS) (Gubler, 1998).

Several species of non-human primates are susceptible to infection with dengue virus. Although infection is asymptomatic, NHPs develop levels of viremia high enough to infect mosquitoes. During the 1970's, Halstead and colleagues conducted various studies in rhesus macaques that had a major impact on the study of disease pathogenesis and vaccine development (Halstead *et al.*, 1973). The development of a recombinant live-attenuated tetravalent dengue vaccine by Sanofi Pasteur, despite questions regarding efficacy (Halstead, 2013), has now reached the final stages of human testing (Sinha, 2014). This work was largely supported by immunogenicity, safety, and efficacy data obtained in NHPs. The vaccine contains four recombinant, live attenuated chimeric viruses comprising a genomic backbone of the replicative genes from the yellow fever vaccine strain 17D (CDY-1-4) and the virion structural genes of each of the four dengue virus serotypes substituted for their yellow fever counterparts. Safety and immunogenicity of CDY-2 was initially tested in rhesus monkeys (Guirakhoo *et al.*, 2000). Macaques became viremic following immunization with the live attenuated vaccine and developed anti-dengue-2 virus neutralizing antibodies. Unlike the unimmunized controls, macaques immunized with CDY-2 did not develop viremia following challenge with dengue-2 virus. However, it was also observed that upon challenge, CDY-2 immunized macaques developed a strong anamnestic antibody response, generally considered evidence of partial protection. On the other hand, complete protection is characterized by no detectable viremia and an absence of an anamnestic antibody response (Halstead *et al.*, 1973; Whitehead *et al.*, 1970). It is not clear whether this observation has a direct link with the lower efficacy observed in clinical trials for the dengue-2 serotype compared to other serotypes on subsequent natural challenge; however, it highlights the potential importance of results obtained in the NHP model for homotypic immunity and the need for further investigation (Halstead, 2013). Immunogenicity against CDY-2 was also evaluated in macaques previously immunized with a yellow fever vaccine to investigate whether pre-immunity against yellow fever could hinder immunogenicity against dengue antigens. Protection of macaques upon dengue-2 virus challenge demonstrated that pre-immunity to yellow fever vaccine did not interfere with the immune response against CDY-2 (Guirakhoo *et al.*, 2000).

The tetravalent version of the dengue vaccine progressed to testing in cynomolgus macaques. Protection against viremia was observed in 98% of NHPs (Guirakhoo *et al.*, 2004). A dominant immune response against 2 serotypes was observed in NHPs after vaccination with a tetravalent formulation that contained equal amounts of each strain, showing immunological interference between serotypes. Various strategies were explored to ameliorate such interference, including: (1) simultaneous immunization with bivalent

complementary vaccines in different arms; (2) sequential administration of bivalent complementary vaccines; (3) pre-immunization with yellow fever vaccine; (4) the modification of formulation by decreasing the ratio of the immunodominant serotype; and (5) administration of a booster immunization one year following primary immunization (Guy *et al.*, 2009). The findings of this study were key for the design of clinical trials in humans, where different vaccination strategies were tested and the importance of a one-year booster immunization was highlighted to achieve seroconversion against all four serotypes (Capeding *et al.*, 2011; Guy *et al.*, 2011; Morrison *et al.*, 2010; Poo *et al.*, 2011). In addition, serum generated during NHP immunization studies with the tetravalent vaccine was used to demonstrate potential cross-protection against different dengue isolates (Barban *et al.*, 2012).

Other vaccine candidates against dengue that have now reached human trials have also used NHP models to evaluate safety and efficacy against infection (Clements *et al.*, 2010; Coller *et al.*, 2011; Osorio *et al.*, 2011; Simmons *et al.*, 2010). Even though the Sanofi Pasteur tetravalent vaccine is still destined for commercial release in the next few years, the quest for correlates of protection and improved vaccine candidates will require the ongoing inclusion of experiments with NHP models (Halstead, 2013).

Group A *Streptococcus*

According to the WHO, group A *Streptococcus* (GAS) is among the top 10 leading infectious causes of mortality worldwide and is responsible for over half a million deaths annually (Carapetis *et al.*, 2005; WHO, 2005). GAS can cause several mild (e.g., impetigo, pharyngitis) and more serious (e.g., necrotizing fasciitis, streptococcal toxic shock syndrome) infections. In addition, repeated GAS infections also lead to autoimmune diseases such as post-streptococcal glomerulonephritis, acute rheumatic fever (ARF), and rheumatic heart disease (RHD) (Carapetis *et al.*, 2005; Walker *et al.*, 2014). Development of a human vaccine against GAS was hampered by reported cases of rheumatic fever in volunteers immunized with streptococcal M protein (Massell *et al.*, 1969). Safety concerns relating to adverse reactions have focused vaccine development efforts towards a safe subunit-based vaccine (Henningham *et al.*, 2013b). In parallel, specific components from GAS have been identified to have the ability to trigger autoimmune reactions (Cunningham *et al.*, 1997; Faé *et al.*, 2005; Guilherme *et al.*, 2006; Van Sorge *et al.*, 2014), and are therefore unlikely to be incorporated into candidate vaccine formulations.

Another hurdle in the development of a preventive GAS vaccine is the >200 different GAS serotypes in circulation (Sanderson-Smith *et al.*, 2014). An effective vaccine should provide wide coverage against different GAS serotypes without triggering autoimmune responses. Researchers have identified several GAS antigens that do not generate cross-reactive antibodies to human proteins, are highly conserved in different GAS serotypes, and have shown protection in at least one mouse model (Bensi *et al.*, 2012; Chiarot *et al.*, 2013; Henningham *et al.*, 2012; 2013a; Pandey *et al.*, 2009; Rodriguez-Ortega *et al.*, 2006; Van Sorge *et al.*, 2014).

Despite the inability of GAS to naturally infect mice, most vaccine candidates have been extensively tested in mouse models using intranasal (Batzloff *et al.*, 2005; Cleary *et al.*, 2004) and intraperitoneal infections (Henningham *et al.*, 2012; Pandey *et al.*, 2009; 2013). Although these models have provided valuable information about potential vaccine candidates, it is necessary to evaluate these candidates in a setting that resembles human infection. There are several reports of the use of NHPs for the study of GAS pathogenesis (Ashbaugh *et al.*, 2000; Gryllos *et al.*, 2001; 2008; Skinner *et al.*, 2011; Virtaneva *et al.*, 2003; 2005). Ashbaugh and co-workers developed an infection model in adolescent baboons that was able to demonstrate the importance of GAS M-protein and capsule in the ability to colonize the pharynx. NHPs with pharyngeal infection developed symptoms and post-infection humoral responses similar to that observed in humans (Ashbaugh *et al.*, 2000). The same baboon model was later used to study the regulation of capsule gene expression during the early stages of infection (Gryllos *et al.*, 2001), and the contribution to virulence of the peroxide stress response regulator PerR (Gryllos *et al.*, 2008). Virtaneva and collaborators used cynomolgus macaques to develop another NHP infection model for pharyngeal colonization (Virtaneva *et al.*, 2003). As with the baboon model, cynomolgus macaques developed clinical symptoms of pharyngitis and developed humoral responses similar to humans (Virtaneva *et al.*, 2003). The cynomolgus macaque model was later used in an infection protocol where researchers were able to link changes in GAS transcriptome with different phases of clinical disease (Virtaneva *et al.*, 2005). Another study by Skinner and colleagues reported the infection of cynomolgus and rhesus macaques for the development of an infection model that could be used to evaluate streptococcal vaccine candidates (Skinner *et al.*, 2011). NHPs have also been used to test immunogenicity of one of the more advanced vaccine candidates against GAS. This vaccine consists of the GAS peptide antigen J8 conjugated to CRM197, a non-toxic diphtheria toxin analog. All immunized NHPs developed antigen-specific antibodies detected by ELISA, which suggests that the vaccine was highly immunogenic. However, the functionality of the antibodies was not assessed and no efficacy/protection studies were reported in this study (Caro-Aguilar *et al.*, 2013). Combined, these studies demonstrate the potential utility of NHP models for GAS vaccine development.

HIV

Human immunodeficiency virus (HIV) has claimed 39 million lives, with approximately 35 million people living with HIV by the end of 2013 and approximately 2 million new cases annually (WHO, 2014). The quest for a preventive HIV vaccine is ongoing. NHP models have been used in HIV research more extensively than for any other infectious pathogen. Experimental infection of rhesus macaques with simian immunodeficiency virus (SIV) results in similar clinical symptoms as those described for human patients with acquired immunodeficiency syndrome (AIDS) (Letvin *et al.*, 1985; Silvestri *et al.*, 2007). The NHP infection model using simian immunodeficiency virus (SIV) or SIV that expresses HIV envelope (SHIVs) has been used to test numerous vaccine candidates. These studies have driven the translation of such vaccines into human clinical trials. However, clinical trials for HIV vaccine candidates have shown disappointing and surprising results (Robb, 2011),

raising questions about the use of NHP models to evaluate vaccine immunogenicity and efficacy (McChesney and Miller, 2013; Shedlock *et al.*, 2009).

Merck developed an HIV vaccine based on replication-defective adenovirus 5 (Ad5) vectors that expressed HIV-1 *gag*, *pol*, and *nef* genes (MRKAd5 HIV-1). Initial testing of the Ad5 vector that expressed the *gag* gene was tested in an NHP model (Shiver *et al.*, 2002). Intramuscular immunization with the viral vector on weeks 0, 6, and 32 resulted in development of antigen-specific $CD8^+$ T cell immune responses and production of INF-γ. Challenge of NHPs by intravenous injection of SHIV 89.6P caused loss of $CD4^+$ T cells during the acute phase of infection in immunized and control animals with comparable viral loads. However, 70 days after challenge, immunized NHPs showed recovery of $CD4^+$ T cell counts and control of viremia. Moreover, during the one-year course of the experiment, five out of six unimmunized NHPs showed various degrees of immunodeficiency-related symptoms, while immunized NHPs remained healthy (Shiver *et al.*, 2002). These positive results obtained in the NHP model suggested that responses to the Ad5-based vaccine could provide control of virus replication, thus encouraged the advancement of an Ad5-based vaccine into clinical trials. During a phase I clinical trial, the MRKAd5 HIV-1 vaccine was delivered to healthy HIV-uninfected adults (Priddy *et al.*, 2008). No serious vaccine-related adverse events were detected during the course of the study and the vaccine showed the ability to induce antigen-specific cellular responses in at least 60% of volunteers that received the MRKAd5 HIV-1 vaccine. These promising results supported progress into phase II trials. Disappointingly in the STEP efficacy phase IIb trial, the MRKAd5 HIV-1 vaccine was not able to prevent HIV infection or control levels of viremia (Buchbinder *et al.*, 2008). More alarmingly, an increased number of HIV infections were reported in a subgroup of patients who received the MRKAd5 HIV-1 vaccine. New NHP studies, carefully designed to mimic the setting of the STEP study, showed that an Ad5-SIV vaccine lacked efficacy against SIV infection when NHPs where challenged via the mucosal route (Casimiro *et al.*, 2010) and enhanced infection rates following a low-dose penile SIV challenge (Qureshi *et al.*, 2012). These studies not only highlight the utility of the NHP model for HIV, but also underline the importance of experimental design and precise interpretation before extrapolating observations from NHP to humans (McChesney and Miller, 2013).

Despite both progress and disappointment, the search for a preventive HIV vaccine will continue with the use of NHP models. The search for vaccine candidates and reliable correlates of protection will continue and the NHP model is a key contributor to this difficult task.

Vaccines for the Elderly

Vaccination has been the most cost effective intervention to reduce mortality and morbidity due to infectious diseases. With some exceptions, vaccines have mostly focused on prevention of childhood diseases. However, the aging world population highlights the need for vaccines that prevent common infections in the elderly.

Development of targeted vaccines for the elderly challenges our current knowledge of vaccine immunogenicity due to immunosenescence, which not only makes aged adults more susceptible to infections but also less responsive to vaccination (McElhaney, 2011; Park and Nahm, 2011). Several studies have shown that rhesus macaques undergo an immune system aging process similar to humans. Aged NHPs show loss of naive T cells, a decreased T cell repertoire (Janković *et al.*, 2003; Messaoudi *et al.*, 2006), and a change in the cytokine profile expressed by peripheral blood mononuclear cells (PBMCs) (Mascarucci *et al.*, 2001).

Old NHPs have been used to study the immune response of aged subjects to various vaccines. Coe and co-workers characterized the immune response against the seasonal trivalent influenza vaccine in young and old NHPs (Coe *et al.*, 2012). Old NHPs developed a significantly lower immune response compared to young NHPs, based on antibody titers. The delivery of a booster after primary immunization increased the secondary antibody response in old NHPs; these responses were comparable to the primary response in young NHPs (Coe *et al.*, 2012).

In addition to the study of immunosenescence, NHP models represent a valuable research tool to investigate novel vaccine candidates and adjuvants that can improve vaccine immunogenicity in the elderly. By using the trivalent influenza vaccine (Fluzone®) in combination with a cationic lipid/DNA complex adjuvant (CLDC), Carroll and colleagues improved overall vaccine immunogenicity in elderly NHPs (Carroll *et al.*, 2014). Aged NHPs immunized using Fluzone®/CLDC mounted antibody responses comparable to juvenile NHPs immunized with Fluzone® alone, and were protected from viral challenge (Carroll *et al.*, 2014).

Other groups have reported the use of elderly NHPs for the study of disease pathogenesis and vaccine immunogenicity studies (Aspinall *et al.*, 2007; Čičin-Šain *et al.*, 2010; Wertheimer *et al.*, 2010). Vaccine development against diseases that affect older individuals such as pneumococcal diseases, varicella zoster, diphtheria, and tetanus would greatly benefit from the use of elderly NHP models. A better understanding of immune response mechanisms, correlates of protection, and potential therapies aiming to rejuvenate the immune system, will have a major impact on the health of an aging population (Aspinall and Lang, 2014; Meyer *et al.*, 2012).

Conclusions

The specific cases reviewed in this manuscript offer important examples of the relevance of NHP models to vaccine research. Vaccine candidates for many other diseases are also being investigated through the use of NHP models, and as our knowledge about the different NHP species and the response to infectious human pathogens and vaccines continues to grow, further applications for NHP models will emerge. Small animal models will remain the workhorse of infectious disease and vaccine research, and we do not suggest NHP models should replace these. Rather, both animal models complement each other to provide a better understanding of vaccine mechanisms of protection and disease pathogenesis. It is important to mention that research must be guided by robust experimental design and careful interpretation of results to garner the full value of NHP models, and that non-human

primates are used only when necessary and only when other animal models are not suitable or have not contributed to the designed investigations in a meaningful way.

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