Experimental primates and non-human primate (NHP) models of human diseases in China: current status and progress

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Abstract: Non-human primates (NHPs) are phylogenetically close to humans, with many similarities in terms of physiology, anatomy, immunology, as well as neurology, all of which make them excellent experimental models for biomedical research. Compared with developed countries in America and Europe, China has relatively rich primate resources and has continually aimed to develop NHPs resources. Currently, China is a leading producer and a major supplier of NHPs on the international market. However, there are some deficiencies in feeding and management that have hampered China's growth in NHP research and materials. Nonetheless, China has recently established a number of primate animal models for human diseases and achieved marked scientific progress on infectious diseases, cardiovascular diseases, endocrine diseases, reproductive diseases, neurological diseases, and ophthalmic diseases, etc. Advances in these fields *via* NHP models will undoubtedly further promote the development of China's life sciences and pharmaceutical industry, and enhance China's position as a leader in NHP research. This review covers the current status of NHPs in China and other areas, highlighting the latest developments in disease models using NHPs, as well as outlining basic problems and proposing effective countermeasures to better utilize NHP resources and further foster NHP research in China.

Keywords: Non-human primates; Experimental primates; Animal models; Current status

Employing animal models for biomedical research has been done to speed along research by bypassing ethical restrictions on using humans as experimental subjects, which averts risks associated with direct research on humans, especially in clinical trials. There are likewise numerous advantages to using animal models such as strong controllability of experimental conditions, high repeatability, ease of scale, comparability of results. However, the effectiveness of animal models is hampered by intrinsic species differences between animal models and humans. For example, experimental data obtained from rodents, who are phylogenetically distant from humans, does not always appropriately predict the efficacy of a drug treatment or its potential toxicity in humans (Van Der Worp et al 2010; Xu, 2011). To bridge the gaps, non-human primates (NHPs) have been widely used in lab settings since the 1950s. There has been a corresponding increase in the prominence and importance of using NHP models that have been widely used as subjects in infectious diseases (Kaushal et al, 2012; Liu & Zhang, 2010), mental and neurological disorders (Perretta, 2009), cardio-cerebrovascular diseases (Sy et al, 2014), and endocrine diseases (Kamath et al,

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2011; Pound et al, 2014), to name just a few.

The key advantage of using NHPs is that NHPs are phylogenetically the most proximate models to humans, bearing many distinctive similarities not found in other animal models. Previous reports found that DNA sequence similarities between NHPs and humans can reach up to 98.77% (Fujiyama et al, 2002) and the concordances rates of gene transcription levels of spleen, peripheral blood monocyte cells (PBMCs) and liver between NHPs and humans can reach as high 91.41%, 84.36%, and 74.29%, respectively (Lu et al, 2008). As a consequence, NHPs remain the first or the only choice for investigating major human diseases including HIV/AIDS, measles, malaria, hepatitis, but also in the study of human cognition and brain diseases (Xu et al, 2013). In addition, NHPs are also used for human cancer research (Xia & Chen, 2011). The data garnered from such NHP experiments is invaluable as a starting point, because it ensures greater efficiency and surety of future clinical application, making NHPs the "gold standard" for preclinical studies (He et al, 2013).

It was half a century ago that the NHP model was gained traction in Europe and America where most of the scientific research were conducted at the time. They began to develop the NHP resources by importing NHPs from other countries, developing husbandry programs and exploring the nature of NHPs. As more recent advances in medical research and biotechnology involving gene modification, gene knockout, epigenetics, precision gene editing and fine regulation of local gene expression in experimental primates become more cost-effective and refined, we expect that there will be greater need for NHP resources to meet the demands of many new applications, which developed countries with advanced knowledge of NHPs may struggle to meet. At this point, countries with indigenous NHPs that can also advance effective protection, sustainable exploitation and utilization of their NHP resources may stand to benefit. Indeed, as its growing life sciences and pharmaceutical industries, China has a great opportunity to become a leader in NHP resources and even research (Cyranoski, 2004; Hao, 2007).

This review evaluates the ongoing situation of NHPs in China and other areas as well as the latest development of human disease models using NHPs in China. We analyze the existing problems for further developing NHP models and propose targeted countermeasures that may allow for better exploitation and utilization of NHP resources in China.

Status of experimental primates abroad

There is a disagreement on the total number of primate species in existence. According to the 2005 Mammal Species of the World (http: //vertebrates.si.edu/msw/mswCFApp/msw/index.cfm), there are 376 primate species. However, the latest statistics from *IUCN Red List of Threatened Species* (http: //www.iucnredlist.org) declare 420 primate species. Occasionally, new primate species are described, such as *Rhinopithecus strykeri* that was discovered recently (Geissmann et al, 2011; Long et al, 2012), make the numbers subject to change. More important to the total number of primates are threats from humans, whose development often interferes with primate habitat. As a result, most primate species are considered to be endangered. To overcome the threats to NHPs, numerous countries have adopted strict protective measures on NHP resources, and some have began to pay greater detail to utilizing these resources more rationally.

While America has no wild NHPs, it is home to primate research institutes including 8 national primate research centers (NPRCs) funded by the National Institutes of Health (NIH) that develop NHP models for basic and applied studies of human health: California National Primate Research Center, New England Primate Research Center, Southwest National Primate Research Center, Tulane National Primate Research Center, Washington National Primate Research Center, Wisconsin National Primate Research Center, Yerkes National Primate Research Center, and Oregon National Primate Research Center (Kaiser, 2013). These 8 NPRCs have a total number of 26, 000 NHPs (Hayden, 2008), representing more than 20 species of NHPs, mostly macaques (largely for practical purposes and ease of research). Annually the US federal government invests about $100 million each year into these NPRCs to financially support ongoing studies of NHPs (http://www.humanesociety.org/animals_in_research/general_information_on_animal_research/an_introduction_to_primate_issues.html). As advances in research techniques and methodology using primate models have been created, there has been a consummate increase in investment. From 1999 to 2006, funding through the US federal government for NHPs research increased 7.9-fold, ($15.4 million to $122 million), while the total number NHPs at the eight NPRCs increased from 24 182 to 27 914 (http: //www.all-creatures.org/saen/res-nprcs-8yr.html). Other

institutions with strong focuses on NHP research also receive federal and state funding, including the New Iberia Research Center at the University of Louisiana at Lafayette, the University of Texas MD Anderson Cancer Center, Alamogordo Primate Facility and Primate Foundation of Arizona, the Caribbean Primate Research Center, a squirrel monkey colony of the University of South Alabama and a baboon breeding facility of the University of Oklahoma. Even a few private facilities in NHP breeding receive government grants to maintain the US's overall capacity for conducting NHP research (http: //www.sourcewatch.org/index.php/National_Primate_Research_Center_System). One further aspect of NHP research in the US worth noting is that the US is home to the largest colony of Chimpanzees used for research, with around 1 000 currently in government sponsored labs (Wadman, 2011a). Chimpanzees are the only great apes known to be captured for biomedical research, even though they are also an endangered species, and given that they are the primates most closely related to humans, are used in invasive research, and defined as "inoculation with an infectious agent and/or drug testing."

Compared to the US, Europe is the next largest center of NHP research (Carlsson et al, 2004), though with some different trends. While the number of NHPs used in experiments in America has grown annually from 2001 to 2010 (Figure 1, data from http: //www.aphis.-usda.gov), the total amount of NHPs used for research in the EU remains lower than in America, without stable growth. Within EU, total NHPs used for research in 2003, 2005 and 2008 were 10 360, 10 450 and 9 600, respectively (https: //www.gov.uk). The most popular NHPs used for research were rhesus macaques (RMs) and cynomolgus macaques (CMs), with pig-tailed macaques, squirrel monkeys, African green monkeys, common marmosets, cotton-topped tamarins, baboons, chimpanzee, among others taking a minor share. No apes were used in experiments anywhere in the EU from 2002−2008 according to a survey by the European Commission (http: //vertebrates.si.edu/msw/mswCFApp/msw/-index.cfm). There is much debate regarding whether National Institutes of Health (NIH) research chimpanzees be retired (Wadman, 2011b) and US primate centre faces scrutiny with stricter criteria (http: //www.-nature.com/news/us-primate-centre-faces-scrutiny-1.10317). In June 2013, NIH announced that it will retire to sanctuary nearly all of its research chimpanzees (http: //blogs.nature.com/news/2013/06/nih-retires-most-research-chimpanzees.html).

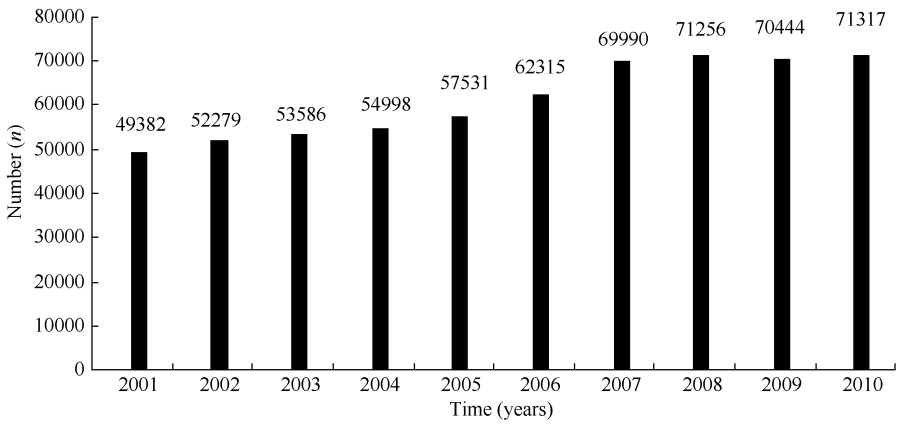

Figure 1 Number of NHPs used in experiments in America per year from 2001 to 2010

While the US and Europe are the key centers of NHP research, Southeast Asian countries that possess indigenous NHPs have recently begun to pay more attention to these resources. Southeast Asia has made rapid advances in its NHP capacity: several NHP research institutions and breeding facilities have been set up in the area, and a few NHP breeding facilities have passed the American Association for Accreditation of Laboratory Animal Care (AAALAC) certification. For example, Thailand has NHP facilities and primate research centers, among which Primate Research Institute of Thailand (PRIT; http: //www.primate.or.jp/se-mi/Abst_f2nd/suchinda.pdf) possesses 14 species of primates, and focuses on primate breeding and producing animal models suitable for diseases research, especially for tropical diseases research. These advances have made

the PRIT a key biomedical research center on primates and an information center for NHPs among Southeast Asia. The presence of such facilities and their corresponding resources greatly enhances the entire region's NHP research capacity, and complements the growth in NHP resources and research being conducted in China.

Status of experimental primates in China

Compared to US and Europe, NHP resources are rich in China. More than 24 species were found. It accounts for about 6% of primate species around the world. Yunnan Province in particular possess the most NHP resources, and undertakes a bulk of the earliest and present work on NHPs (Shen & Yang, 2003; Pan & Ben, 1984; Li & Lin, 1983). The anchor institution of this research, Kunming Institute of Zoology (KIZ), Chinese Academy of Sciences (CAS), was established in the late 1950s. KIZ is among the first institutions in China to start a primate breeding center to conduct basic research and clinical applications on NHPs in taxonomy, ecology, anatomy, genetics, behavior, evolution, reproductive biology, neurobiology, immunology, and with a series of laboratories dedicated to animal microbial detection, animal nutrition, clinic pathology of animal; KIZ has also produced a series of monographs on NHPs including *The Anatomy of the Golden Monkey*, *The Anatomy of Macaca mulatta*. The primate centre in KIZ hosts currently about 2 800 NHPs, including *M. mulatta, M. leonine, M. fascicularis, M. assamensis, M. arctoides, Rhinopithecus roxellana,* and other species. The facility is well-equipped to deal with these NHP resources, as it has received AAALAC certification, and the centre's NHP resources and research has received a worldwide attention (Cyranoski, 2004; Hao, 2007). Alongside KIZ, Institute of Medical Biology (IMB), Chinese Academy of Medicine Science, which was set up in 1958 and before 1980s hosted the greatest number of RMs in China (Shen & Yang, 2003), focuses on the research and development of medical products using experimental primates, particularly for vaccines. IMB is currently the largest base of the research and production of both attenuated poliovirus oral live vaccine and hepatitis A vaccine in China.

Prior to China's development of domestic NHP research into exploitation and utilization of NHP resources, China was—and remains—a leading producer and a major supplier country for NHPs to the United States, Europe, Japan, and now Korea. In 2013, the number of breeding experimental monkeys in China, mainly rhesus macaques and cynomolgus macaques, in China there were about 250 000 breeding cynomolgus macaques and 40 000 breeding rhesus macaques (data from The China Laboratory Primates Breeding and Development Association), with approximately 50 000 to 60 000 experimental monkeys born in breeding facilities each year. Though many NHPs are used for domestic research projects, a large number are exported abroad. For example more than 65% of the experimental monkey imports in the US from Asia are from China, and in Europe, around 70% of research primate imports are from China. Essentially, though NHP research remains predominately a Euro-American venture, China is the leading supplier of resources necessary to this research.

To support China's shift from an NHP resource producer to an NHP research driver, the Chinese government has increased investment for experimental primates and new drug development. Over the last decade, there has been marked progress on research and innovation into experimental primates. Specifically, the Ministry of Science and Technology (MOST) of the People's Republic of China has set up an experimental primate germplasm resources center in Hainan and Suzhou, and in 2011 MOST launched a number of large science projects under the platform construction of promoting the development of primate animal models of human major diseases. The General Administration of Quality Supervision, Inspection and Quarantine of China has likewise set up a state key laboratory for experimental primate animal quarantine in Guangxi Province, and as we mentioned previously the CAS established the Kunming Primate Research Center of Chinese Academy of Sciences in Yunnan. In addition, the governments are providing more support and financial resources to NHP research. In short, these actions will undoubtedly accelerate the innovation and capacity for NHP research in China. Prior to 2005, most high-quality experimental NHPs were exported to European, America and other "developed" countries, while the domestic consumption was relatively limited, but thanks to the additional support and development of the Chinese scientific community, outsourcing of services related to experimental NHPs have continued to spring up and domestic services have exploded in Beijing, Kunming, Shanghai, Suzhou, Chengdu, Guangzhou, among others, to improve the development of experimental NHPs in

China.

Current status and progress on the NHP models of human diseases in China

Chinese researchers have established numerous NHP models to model a variety of human diseases, which have made large contributions to the study, prevention and treatment of human diseases. In China, most NHP models for human diseases focus on exploring infectious diseases, cardio-cerebrovascular diseases, endocrine diseases, reproductive diseases, mental and neurological disorders, and ophthalmic diseases. Similarly, some basic research into NHPs by Chinese researchers have greatly extended the usability of NHPs as animal models by exploring transgenic strategies in experimental primates and in 2010 researchers of Kunming Institute of Zoology, CAS created the first transgenic monkey in China (Niu et al, 2010).

Primate animal models for infectious diseases

Though advances in medicine and medical technology have effectively controlled or eradicated infectious diseases, a variety of new infectious diseases have continuously emerged, largely as a result of human activities' adverse impact on the surrounding environment and bringing individuals into closer contact with these situations. As a developing country with the world's largest population, China is actually threatened by many infectious diseases that are exacerbated by population density, intense land-usage, and industrialization, such as HIV/AIDS tuberculosis (TB), viral hepatitis, foot-and-mouth disease, avian influenza. This problem is only magnified on the global scale, especially among developing countries that experience the bulk of population growth and the increase in population densities as a consequence of urbanization and industrialization. Given the nature of infectious diseases and the larger global trends, developing more ideal and targeted animal models is a crucial step for opening up new strategies against them.

HIV/AIDS

To our knowledge, no animal models for HIV/AIDS research are more suitable than NHPs. HIV-1, for instance, infects only humans and a handful of primate animals such as the chimpanzee, gibbon and pigtailed macaque (Kuang et al, 2009). While HIV-1 can infect these NHPs, for several reasons the disease's progression is quite different from that in humans, though AIDS models of RMs infected with SIV closely resemble the human disease progression of AIDS. Consequently, NHPs are the most widely used animal models for HIV/AIDS research (Lei et al, 2013). Though NHP AIDS models were established using simian retrovirus (SRV) in the early years, NHP AIDS models created with SIV better simulate human AIDS. Currently, most NHP AIDS models in China for developing vaccines and therapeutics are established via infection of SIV or SHIV, a simian/human immunodeficiency chimeric virus.

An initial Chinese RM/SIV model established by Li et al (2007) was accomplished by infecting Chinese RMs with SIVmac239. Furthermore, Xia et al (2010, 2011) and Li et al (2012) investigated the dynamic and functional changes of dendritic cell subsets and Treg cells in SIVmac239-infected Chinese RM. The results confirmed a previous study and showed that disease symptoms of SIV-infected Chinese RMs were more similar to human responses to HIV-1. Feng et al (2007) also set up RM models of SIVmac251 infection using several different routes (intravenous, intravaginal and intrarectal routes) and observed differences in disease course after SIVmac251 infection resulting from the different routes; notably, this was the first case of a Chinese NHP AIDS animal model infected with SIV through a mucosal route. Later, Cong et al (2011b) established a Chinese RM model of SHIV-$_{SF162p3}$, an HIV-1 subtype B, infected through repeated low-dose intravaginal inoculation, which more closely resembles the natural transmission of HIV infection in humans. Though HIV-1 subtype C comprises the predominant strains in China (Wu et al, 2006), Cong et al's model provides technical reference for establishing further AIDS animal model for evaluating vaccines and treatment strategies suitable for China's predominant epidemic strains, which may change given growing infection rates and variances, especially in Yunnan. Additionally, researchers have also successfully established different HIV domestic Chinese RM models (Wang et al, 2011b; Cong et al, 2011a; Yao et al, 2011). The characteristics of these models remains to be elucidated in future, however, as HIV/AIDS infections continue to increase globally in general and in China (and Yunnan) in particular, these models may become increasingly important research models.

While the existing SIV/SHIV-infected macaque models are useful for application in AIDS research, genetic differences between SIV/SHIV and HIV-1

significantly limit the use of SIV/SHIV (Ambrose et al, 2007; Van Rompay, 2012). Accordingly, NHP AIDS models established with HIV/HSIV infection should be a better model of human HIV/AIDS infections and pathology; fortunately, researchers at the KIZ are currently establishing northern pig-tailed macaque AIDS model with HIV/HSIV. If successful, such a novel model may provide an ideal platform for the study, drug screening and the vaccine evaluation of AIDS.

Tuberculosis (TB)

Recent studies reveal that mouse models are quite questionable, but NHP models avoid many of the pitfalls that make rodent models less popular; in particular, NHP models of TB for immunological research and vaccine test show promising results (Kaushal et al, 2012; Guo & Ho, 2014). The study of NHP models of TB was later than other countries in China, despite the ongoing prevalence of the disease. For TB, there is a certain gap in the types and construction methods of NHP models, for example, the NHP models of TB latency and reactivation have not been done in China.

Currently, there are several reports on the ongoing construction of NHP models for TB study in China. For instance, Wuhan University began to establish of NHP models of TB using fiberoptic bronchoscopes since 2006, and later delivered *Mycobacterium tuberculosis* (MTB) into the lungs of Chinese RMs (Xian et al, 2010; Zhang et al, 2011a). This laboratory has become the fifth standard laboratory for TB vaccine study in the world (http: //news.sohu.com/20060715/n244270131.shtml), and models have been used in preclinical testing of candidate vaccines and drugs. Wang et al (2012) later established Chinese RM models of TB via bronchoscopic and intratracheal instillation into the lungs and found the clinical manifestations, disease progression and pathological changes of these models closely resembled human primary TB and hematogenous disseminated TB.

NHP models of TB have marked advantages in immunological research and test of drugs as compared with non-primate models. Unfortunately, the lack of currently available inbred strains of NHPs makes pathological changes varied. The obvious solution is to strengthen the system research of pathological features, such as lobe fibro-cavitary lesions, etc. Likewise, studies suggest that there is a high rate of HIV and MTB co-infection, which is thought to be one of factors contributing to the global resurgence of TB (Harrington, 2010; Kaushal et al, 2012). In theory, infection with HIV accelerates the activity of latent MTB and then increases the incidence of TB and, at the same time, TB seems to speed the HIV replication rate (Enserink, 2001), making them a potentially lethal complication. Establishing NHP models of TB then provides a foundation for the constr-uction of NHP models of MTB/HIV co-infection, which may prove more ideal than NHP models of MTB/SIV co-infection (Diedrich et al, 2010) currently in place.

Influenza virus

Of the many infectious disease pandemics, infl-uenza has been one of the worst (Kilbourne, 2006). This is especially poignant for China, as outbreaks of highly pathogenic H5N1 avian influenza viruses occurred in Hong Kong in 1997, killing 6 people (Mounts et al, 1999), which was the first worldwide report of avian influenza virus directly infecting humans. Following the report, avian influenza A infection in humans was also reported in Southeast Asia, Europe and North Africa (Obenauer et al, 2006), and outbreaks of H7N9 in humans in China last year received local and global attention (Gao et al, 2013a, b; Hu et al, 2013; Liu et al, 2013). Since rodent animals are not the natural hosts of influenza viruses and show no symptoms of upper-respiratory-tract infections (Zak & Sande, 1999), rodent models are not good systems for studying human influenza infections. NHP models are, however, excellent at mimicking human infections of influenza viruses. Foreign researchers have established NHP models infected with H1N1, H3N2, H5N1, etc (Baas et al, 2006; Carroll et al, 2008; Cillóniz et al, 2009; Fan et al, 2009; Itoh et al, 2009; Kobasa et al, 2007; Laddy et al, 2009; Rimmelzwaan et al, 2001). Recently, Chen et al (2009) infected Chinese RMs with the highly pathogenic avian influenza virus A/Tiger/Harbin/01/2002 (H5N1) intrana-sally and noted that RMs exhibited symptoms similar to humans, such as fever, loss of appetite, interstitial pneumonia, etc. These results indicated that Chinese RMs could be potentially successful infection models of the H5N1 viruses as they exhibit similar symptoms. To date, this model has some shortcomings, since H5N1 only reproduced in the respiratory system and that RMs showed low sensitivity to H5N1 infection. In view of these limitations, Lü et al (2011) infected Chinese RM with A/SZ/406H/2006(H5N1) by endotracheal incuba-tion, and found that this method yielded a more sensitive NHP model of H5N1 virus infection, and that the virus

could replicate in many other organs outside the lung and better resembling severe cases seen in humans.

Since the influenza virus is primarily transmitted via air, it is necessary to assess the contributions of small droplet aerosols and larger respiratory droplets to better understand epidemiological vectors for the disease and public responses to influenza virus outbreaks. Technological hurdles currently make it difficult, such as lack of inoculations for influenza viruses in NHPs and the difficulty in isolating and quantifying viable influenza viruses from dilute aerosols make this currently impractical.

Hepatitis virus

Compared to other infectious diseases, China has a long history of research into hepatitis. Over 30 decades ago, Ge et al (1989) performed long-term liver biopsies of *M. assamensis*, *M. Speciosa, Nycticebus Coucang* infected with HBV, successfully setting up NHP models of HBV infection. Zhang et al (1998) infected RMs with HGV and established the first RM model of HGV infection, while more recently Yang et al (2006) infected Chinese RMs with HEV gene type-IV via intravenous injection. Following Yang's injection, Chinese RMs exhibited typical acute hepatitis, indicating Chinese RMs made viable animal models of HEV gene type-IV. Chinese researchers also successfully established Chinese RM models of HEV1 infection, and through these models found E2 IgG can serve as a marker of HEV infection (Zhang et al, 2003; 2004).

Chinese researchers have used HAV, HBV, HEV and HGV to infect NHPs (Ge et al, 1989; Zhang et al, 1998; Zhang et al, 2003; 2004). But there have been no reports of the establishment of domestic NHP models for HCV infection. Chimpanzee models of HCV infection have already been established by foreign researchers, though this is expected since chimpanzees are the only known animal to be susceptible to HCV infection (Bukh et al, 2001). However, ethical and financial restrictions largely limit the use of chimpanzees for such research, especially in the US and Europe (Akari et al, 2009). GBV-B, a close relative to HCV, provides an effective model and has been used to infect New World monkeys and the GBV-B infection models which closely resemble HCV infection in humans (Akari et al, 2009; Bukh et al, 1999). In spite of the value of the GBV-B model, the establishment and development of an HCV/GBV-B chimeric virus model has higher application value for a preclinical study of antiviral vaccines and drugs, and accordingly foreign researchers have created monkey models infected with an HCV/GBV-B chimera (Li et al, 2014; Rijnbrand et al, 2005). In future, we should focus on developing NHP surrogate models for HCV infection.

Enteroviruses

Enteroviruses (EV) affect millions worldwide each year. The enterovirus is a genus of RNA viruses associated with several human diseases, and among them Enterovirus 71 (EV71) is highly contagious and causes foot and mouth disease (HFMD) , which has increasingly been a serious threat for Asian children (Lee & Chang, 2010). CMs infected with EV71 via lumbar injection or intravenous route show some symptoms similar to those found in humans, but these CM models do not exhibit certain important infection symptoms, such as myocarditis and neurogenic pulmonary edema. Likewise, most of the EV71 applied to these CM models are host-adapted EV71 strains (Hashimoto & Hagiwara, 1982; 1983; Hashimoto et al, 1978; Nagata et al, 2004; Nagata et al, 2002), and there can be marked differences between host-adapted EV71 strains and the epidemic strains. Unfortunately, NHPs are not susceptible to infection with epidemic strains of EV71 (Liu & Zhang, 2010).

The study of EV71 infection NHP models began relatively late in China, with the first models appearing in 2010. Zhang et al (2011b) infected adult Chinese RM with EV71 FY-23 strain via intracerebral, intravenous, respiratory and digestive routes and showed similar symptoms to human cases but without herpetic lesions, the reason for which may be old-age of these experimental Chinese RMs. Perhaps neonatal monkeys would prove better animal models for the study of EV71 pathogenesis, and accordingly Liu et al (2011) infected neonatal RMs with EV71 FY-23 strain via the respiratory tract by tracheoscopy and the results indicated these neonatal RM models more closely resembled infection of human neonates during lactation. Wang et al (2011a) likewise infected neonatal RMs with EV71 via nasal spray, which further confirmed that a respiratory infection route makes models more susceptible to EV71 infection than the digestive tract infection route, providing some valuable information for future studies of childhood EV71 transmission.

NHP models of cardio-cerebrovascular disease

Myocardial infarction, a type of cardiovascular

disease, has high morbidity and mortality, and is common in Europe and America (Yeh et al, 2010). Previous studies indicated that the treatment strategy—proved to be effective in a murine model—applied to NHPs failed to show any efficacy (Norol et al, 2003; Orlic et al, 2001). Yang et al (2011) recently established RM models of myocardial infarction by ligating the left anterior descending artery (LAD) and the changes of histopathology and electrocardiogram demonstrated that this model should be excellent for studying human myocardial infarction, but the main cause of myocardial infarction in human is cardiovascular blockage or spasm caused by the long-term effects of several factors (hypertension, hyperlipidemia, etc.). The pathogenesis of these RM models created by ligation of the coronary artery existed many differences compared with human, which currently limits drug discovery and development. It is necessary that new NHP models should be developed for studing human myocardial infarction in future.

Cerebrovascular disease is the second leading cause of mortality in China. Ischemic cerebrovascular disease accounts for 80% of cerebrovascular diseases (Feigin et al, 2003). Pan et al (2006) injected polyvinyl alcohol into a branch of middle cerebral artery to make thrombed, and CT scanning and related behavioral changes showed significant damage to brain tissue in the area of vascular occlusion. These results indicate that NHP models of ischemic cerebral infarction were successfully established and they owned good stability and were suitable in the study of treating acute and chronic diseases. Zhu et al (2008) also established CM models of photochemical thrombosis by focusing the cold lamp-house on the precentral gyrus, and the construction of these models is simple and highly reproducible, making them excellent for the basic study and investigation of treatments for cerebral infarction, especially regarding the study of transplantation of stem cells. Xu et al (2012) recently generated Chinese RM models of middle cerebral artery occlusion by injecting auto-blood clots into middle cerebral artery through the femoral artery with a microcatheter, a method that is easily repeatable, with high stability and low mortality. Likewise, the extent of embolization of the cerebral infarction could be timely detected. The aforementioned advantages have led to this technique becoming more common and ideal for the study of cerebral ischemia. Zhu et al (2009) previously established CM models of intracerebral hemorrhage by injecting antiautologous blood slowly and gently into the caudate nucleus. This study indicated that the volume, site and speed of injection are key factors for establishing a successful model, which is instructive to development of the NHP models of intracerebral hemorrhage.

While there has been significant progress in establishing NHP models of cardio-cerebrovascular disease, some shortcomings still exist. The NHPs chosen to be animal models for cardio-cerebrovascular disease are usually young and healthy, despite the fact among humans the elderly are at the highest risk for cardio-cerebrovascular disease (Baccini et al, 2008). Similarly, the patients with cardio-cerebrovascular disease usually suffer from other health conditions such as hypertension, hyperlipidemia or diabetes which may significantly affect cardio-cerebrovascular symptoms. Currently available studies of NHP models of cardio-cerebrovascular disease that accompany these additional diseases is quite limited, to create viable NHP models of cardio-cerebrovascular disease which is close to clinical nature will be our future task.

NHP models of diabetes

Diabetes is already quite prevalent in developed countries, mainly type 1 and type 2, and it is quickly rising in China now, with an estimated 11% of the population currently afflicted to some extent. Although rodents have been used as the primary model in studying diabetes, rodent models do not adequately mimic human diabetes and make them quite limited for clinical application (Anderson & Bluestone, 2005; Delovitch & Singh, 1997). NHPs, due to their similarities with human, are believed to be the most effective models for human diabetes.

NHP diabetic models are relatively new in China. Liu et al (2009) divided the Chinese RM into a 125 mg/kg STZ group, a 75 mg/kg STZ group and a 50 mg/kg STZ group and then different doses of STZ were injected into corresponding subjects intravenously. The models induced by the dose of 125 mg/kg and 75 mg/kg STZ were not stable, and mortality was high due to the toxic effects of STZ. Most subjects in the 50 mg/kg STZ group retained a high level of blood glucose and their pancreas β cells were severely damaged, but their mortality was quite low, suggesting that 50 mg/kg of STZ may be optimal for inducing diabetes in Chinese RM models. Xu et al (2009) likewise injected STZ at the dose of 45mg/kg into the CMs intravenously and found

that drinking volume, food intake, urine output increased and body weight was reduced, while fasting glucose was increased and the pancreas showed atrophy and fibrosis, indicating that the CM diabetic models created with this method were viable. Given the serious toxic effects of STZ on experimental NHPs, Qiao et al (2009) and Jin et al (2010) established RM models of type 1 diabetes by the partial pancreatectomy combined with low-dose STZ. This strategy is generally safer and more reproducible as compared with single high-dose STZ or total pancreatectomy.

Currently, the most commonly used method to make type 2 diabetic animal models is high fat feeding combined with drugs induction. Typical clinical features of type 2 diabetes was found by injection of STZ into CM at a dose of 35 mg/kg after the appearance of hyperlipidemia and obesity based on high-glucose and fat diet feeding, (Lu et al, 2013) and the models showed. Since pathogenesis of type 2 diabetes induced by STZ is unnatural as it significantly differs from the pathogenesis of human type 2 diabetes, theoretically, screening of monkeys for spontaneous diabetes would lead to a more natural pathogenesis in NHP models. It will make this model more valuable for translational medicine. Wang et al (2004) previously screened 3 RMs of spontaneous diabetes from 100 RMs by both the glucose tolerance and glycosuria tests. These 3 RMs were in middle and elderly age, indicating that onset age and the morbidity rate of spontaneous diabetes in RMs is consistent with that found in humans. After one year of observation, the similarity in clinical symptoms (urinating more and consuming more aggravated gradually and fasting blood glucose was significantly higher than normal) to humans suggested this method was feasible for screening RM models of spontaneous diabetes. Unfortunately, the current number of spontaneous diabetic NHP models is limited and cannot adequately meet the growing demand for effective scientific research.

Given that the morbidity rate of human type 2 diabetes increases annually as long as increases in the number of obese people (mainly caused by factors such as eating patterns, among others), monkey models of type 2 diabetes induced by diet can be accomplished more quickly, and compared with models induced by drugs, more closely resemble the pathogenesis of human type 2 diabetes. Zhang et al (2012) recently divided 36 experimental CMs into 4 groups and fed them standard basic diet, high-sugar diet, high-fat diet and high-sugar combined with high-fat diet respectively for 24 months. The progression of type 2 diabetes among CMs with high-energy diets showed that similar methods were successful in establishing NHP models of type 2 diabetes, and that it effectively modeled different stages of type 2 diabetes. These findings also provided data on further optimizing dietary strategies that could establish even more effective animal models for human type 2 diabetes research. While type 2 diabetic mouse models have been made (Kadowaki, 2000), the successful establishment of transgenic NHP models of type 2 diabetes should vastly improve NHP study of type 2 diabete.

NHP models of mental and neurological disorders

To our knowledge, none of animal models can fully recapture the neurological symptoms for neurodegenerative and psychological disorders due to their multiple origins. While NHPs are close to human in terms of genetics, there are numerous differences in the evolution and composition in brain. Currently, NHP models of mental and neurological disorders such as heroin addiction, morphine addiction, Parkinson's disease (PD), depression syndrome, Alzheimer's disease (AD), spinocerebellar ataxia, spinal cord injury, motor cortex lesion, epilepsy, etc (Chen et al, 2013; Chu et al, 2014; Ding et al, 2008; Liu et al, 1992; Lu et al, 1999; Qiao et al, 2007; Tian & Ma , 2014; Zha et al, 2006; Zhang et al, 1999) have been established in China. However, there is a gap in the types of NHP models for mental and neurological disorders as compared with similar models established in other countries.

An increased understanding regarding natural and artificial repair of central nervous system injuries as resulted as more researchers have begun focusing on the study of nerve regeneration following spinal cord injuries. To model these injuries in NHPs, the main strategy is to inflict spinal cord injury via selective resection of the spinal cord with a sharp knife (Tian et al, 2010). Ni et al (2005) made NHP models of spinal cord hemisection by T-11 laminectomy and then resection of a 1-mm long hemispinal cord, while Zha et al (2006) made the C3-5 exposed via a dorsal midline incision in the neck of RMs and transected the left hemispinal cord with a knife under the microscope after C4 laminectomy. The results showed this method to establish RM models of spinal cord injury were simple, effective, stable, accurate and repetitive, even if the method was quite different from naturally occurring human spinal cord injuries. For

epilepsy, models are usually created by the intentional application of penicillin, aluminum hydroxide, metrazol and coriaria lactone. Chen et al (2013) injected kainic acid into the right intra-hippocampus of RMs by the stereotacic technique, and the resulting seizure pattern, imaging observation and histopathologic tests showed this model closely resembled human temporal lobe epilepsy. Though promising, the long-term stability of this RM models induced by kainic acid requires further study.

Modeling PD has likewise been met with several successes in China. Liu et al (2006) injected 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) into right side internal carotid artery and then performed behavioral testing and imaging detection, which showed the method to be both safe and simple for establishing of NHP models of PD. However, this method made it difficult to control the extent of nigrostriatal damage (Herrero et al, 1991). In order to minimize the nigrostriatal damage, Yan et al (2014) established a chronic NHP model of PD by intramuscularly injecting MPTP. The time of appearance and the severity of each symptom of this model could be controlled by the daily dosage and frequency. This model gradually displayed PD symptoms and mimicked the development of human PD well. However, the PD symptoms were reversible in some MPTP-induced model, being quite different from the degenerative nature of PD in humans, and limiting the study of stem cell therapy for nervous system disorders. Interestingly though, substantia nigra neurons damage caused by 6-hydroxydopamine (6-OHDA) is irreversible, and the extent of nigrostriatal damage can be controlled by the injection amount and the injection sites. Accordingly Zhang et al (2006) generated RM models of PD by injecting 6-OHDA stereotaxically into the right substantia nigra. In testing potential treatments of PD, optimal treatment period is a key issue, and one that can be addressed using NHP models of early stage PD. Accordingly, Ding et al (2008) established NHP early stage models of PD by surgery to make the common carotid artery (CCA) of RMs exposed and then injecting low-dose MPTP into the exposed CCA. Compared with late-stage PD NHPs, NHP early stage models may better mimic the gradual development of human PD. One of the purposes of model development is to find new treatments. Yan et al (2014) reported that morphine could alleviate tremors in a MPTP-induced NHP model, suggesting the therapeutic effects of morphine complement those of L-Dopa, a classic therapy, on PD symptoms. But due to MPTP toxicity to the digestive system, digestive system disorders of the NHP models induced by MPTP gradually appeared and would affect immune function and nutritional metabolism. Such models are difficult to maintain over long durations, making the future development of a long-term stable NHP PD models an urgent issue.

Recently, studies have established a link between increased endogenous formaldehyde (FA), a methanol metabolite, and AD pathology (He et al, 2010; Li et al, 2008; Tong et al, 2011, 2012). Studies conducted by Hu and He's Labs in China on RM showed chronic feeding 3% methanol *ad libitum* led to specific damages to the brain similar to those of Alzheimer's disease. These were the first studies to show that methanol toxicity inflicted all the major hallmarks of AD on rhesus monkey: cognitive decline, tau phosphorylation, and amyloid plaques formation (Yang et al, 2014).

Recent advances in optogenetic technology of have been proved as a revolutionary tool for studying neural systems. Optogenetics can be used for precisely targeting a specific area of neural systems as well as even in freely moving mammals. Researchers can then turn different neurons on or off, rapidly and safely, using this technology (Deisseroth, 2010; Liu & Tonegawa, 2010). Currently, research of optogenetic approaches has been done on NHPs by foreign researchers and some progress of this research has been made (Dai et al, 2013), but there is lack of such research being done domestically in China.

NHP models of ophthalmic diseases

Ophthalmic diseases present interesting complications for animal models. Compared with other animals, the NHP visual system is closer to that of humans than any other animal, making experimental data from NHPs safer and more effective when translated into clinic settings. However, both cost restrictions and availability of experimental NHPs hamper the development of NHP models of ophthalmic diseases. Chinese researchers have successfully established several NHP models of ophthalmic diseases, such as corneal endothelial injury, amblyopia, glaucoma and so on (Dai et al, 2005; Zhu et al, 2013), but there are some gaps in the types and construction methods of NHP models of ophthalmic diseases between China and other developed countries.

Zhu et al (2013) established NHP models of corneal

endothelial injury by phacoemulsification damaging corneal endothelial cells. This method proved easy to manipulate and is easily replicable, and it causes negligible damage to other tissues, making it a useful technique for constructing models that can accurately evaluate the effect of drugs and other factors on the endothelial healing. Similarly, Dai et al (2005) established NHP models of chronic hypertensive glaucoma by semiconductor frequency-doubled 532 laser and argon laser, respectively, aiming at 360° functional trabecular meshwork. The light coagulation times of the successful induction of high intraocular pressure in RMs fluctuate greatly, so refining the existing methods of photocoagulation should improve modeling efficiency, though this requires greater study to verify.

NHP models of reproductive diseases

Reproductive diseases seriously affect human health and even psychological well-being. Infertility caused by reproductive diseases affect an average 8-12% of couples worldwide (Sellandi et al, 2012), and is quite pronounced in developed countries. Reproductive physiology of NHPs is quite similar to human, and the data gathered from studies on reproductive diseases in human using NHPs cannot be replaced using any other experimental animals. The progress in the establishment of NHP models of reproductive diseases, such as polycystic ovary syndrome (PCOS), oligozoospermia, metrorrhagia and postpartum hemorrhage (PPH), has been made by Chinese researchers.

Tang et al (2012) gave RMs two cycles of subcutaneous injections of propionic acid testosterone (PAT), and then muscle injections of human chorionic gonadotropin (HCG). The results of this study indicated PAT combined with HCG could successfully induce RM PCOS, which was similar to human PCOS. Sun et al (2006) earlier set up an RM model of oligozoospermia induced by orally administered gossypol acetic acid and provided a suitable NHP model for the study of infertility in men. Until recently, most studies on PPH still were built on the retrospective analysis, with few reports evaluating or using animal models of PPH. Notably, Huang (2010) established CM models of PPH with uterine atony induced by medication such as oxytocin, which provided a useable platform for further research. Likewise, You et al (2003) had earlier set up RM models of metrorrhagia induced by endometritis and the symptoms of this model could closely resemble those of human metrorrhagia caused by endometritis.

Problems, Challenges and prospects

While China is a key producer of NHP resources, it still lags behind other countries in its capacity for innovative NHP model research. As medical research and biotechnology advances—genetic modification, gene knockout and cloning, etc.—it is likely that a remarkable increase of NHP resources will be developed to meet the needs of more intensive and diverse application. It makes for some interesting possibilities in NHP research. Due to the economic crises and the subsequent "austerity" in budgets across developed countries in America and Europe, funding support for primate research is reduced or kept stagnant. Concurrently, growing criticism from animal-rights activists in these countries has brought a great deal of pressure and research institutions have to limit or even abolish primate research (Cyranoski, 2003; Wadman, 2011b). Given the advances and advantages provided by using NHP primates, researchers on NHP models from developed countries are increasingly seeking collaborations with primate research institutes in China and other developing countries in Southeastern Asia (Cyranoski, 2004). It is possible to bring unprecedented opportunities and challenges to life sciences and biomedical research in China. The key issue is how to cope with these opportunities and challenges to further develop NHP resources effectively.

Development of domestic Chinese NHP resources has made significant progress since its inception, however, in contrast to countries in America, Europe and East Asia (notably Japan and Korea), NHP resources in China are not widely or effectiely being used. In other words, while China has a rich diversity of species, many factors such as subspecies and geographical distribution of NHP resources, differences among subspecies in genetics and physiology and the occurrence of subspecies hybrid populations in breeding and over the course of experiments make the reproducability of experimental results poor in working towards etablishing of animal models, evaluating drugs, etc. Nontheless, some common experimental primate resources (especially exotic species such as *Cercopithecus aethiops*) are rare or even non-existent in China, which restricting human diseases research and the development of corresponding drugs, but other more general factors such as technical skill, experience, and existing resources are also critical. We must realize that Chinese NHP research

can only be accomplished by bringing important experimental primates lacking in China—and researchers familiar with them—while simultanesouly strengthening the application existing experimental primates resources in China.

Another factor making Chinese NHPs ineffective is a lack of the principle knowledge about NHPs. For example, compared with some experimental primate species such as Indian RMs, common experimental primate species such as Chinese RMs lack sufficient information regarding the genetic background of these primates, and it is also little known about the normal value of their important biological parameters (Xia et al, 2009). Thankfully, recent genome sequencing and analysis of CMs and Chinese RMs offers a great deal more basic data and useful reference points for relevant NHP model research (Yan et al, 2011). It is necessary to complement basic biological data of experimental primates in China and establish subspecies breeding populations whose basic biological data (such as genetic backgrounds) are definite. Recently, the Kunming Primate Research Center is making efforts to raise a northern pig-tailed macaques (NPMs, *M. leonina*) colony and Prof. Zheng's lab has collected many basic biological data of this colony of NPMs (Pang et al, 2013; Zhang et al, 2014), in order to promote the standardization and reliability of experimental primate data.

Another key issue for NHP research is the demand for specific pathogen-free (SPF) experimental animals. SPF animals are in great demand right now. While it is available for many traditional models, experimental primates often carry zoonotic pathogens which not only pose health risks to experimenters but also partly interfere with experimental results. In the US, all 8 NPRCs funded by grants through NIH can offer SPF experimental animals (Zheng, 2012), but to date China has not established SPF core groups of experimental primates. Presuming that research into drug development and microbe research on diseases such as HIV continues to grow, if China wants to be a leading player in NHP models, it must establish SPF core groups of experimental primates and all breeding efforts should be done only with careful caution and planning.

In recent years, experimental primate husbandry in China has experienced rapid development and the product has been increased, but not always in tandem with the demand. As we mentioned earlier, the influence of the global economic crisis in developed countries in 2008 as well as interference from animal-rights activists have led to a plateau in primate imports from China. On the Chinese side, this unexpected lack of growth has led to rampant overproduction. Likely one reason for Chinese overproduction is that many NHP breeding facilities in China lack effective communication with their international counterparts, making it difficult to project and then match demand. To remedy the situation and ensure adequate supply of relevant and in-demand NHP resources, it is vital to establish an information and communication platform that can effectively offer NHP breeding information services and simultaneously carry out strategic plans for cooperation between NHP breeding facilities and relevant governing bodies and institutions.

Two other factors could affect China's position on NHP research and supply. First, animal welfare activists have had some effects on NHP research. While it is true that advocacy of animal welfare helps promote harmony between experimental animals and humans (and consequently decreases the danger of injuries to experimenters and often offers higher-quality experimental results), animal welfare has begun to attract extensive attention which will result in increased legislation on animal welfare. China has just recently begun to legislate animal welfare. On a cultural level, Chinese citizens' awareness of animal welfare is weak. Awareness of animal welfare has placed economic pressure on NHP breeding facilities and research institutions. The dual-faced nature of this dilemma means that effective implementation of experimental primate welfare in China is difficult. To bring China more in line with international standards while continuing to develop China's domestic research capacity, relevant policies should be made for strengthening propaganda, supervision, regulation and support of experimental primate welfare, in such a way to support the healthy development of the life sciences and medical industry in China. Second, it is a very crucial step to develop transgenic NHP resources. Since the birth of the first transgenic mouse, researchers have established a series of transgenic mice for modeling many types of human diseases. Transgenic mice have made greater contributions to the study and the treatment of human diseases, but their phylogenetic distance to humans hampers the usefulness of their results. Establishing primate transgenic models should be able to overcome these limitations and better predict the efficacy and toxicity of novel treatments in humans. The

development of these transgenic primates is still in its infancy; the first transgenic primate was born in 2001(Chan et al, 2001), and over the past decade, few transgenic NHPs have been born (Chen et al, 2012). The major obstacles in producing transgenic NHPs are technical in nature. However, thanks to more efficient gene-editing techniques involving ZFN, TALEN and CRISPR/Cas9-based methods, researchers can avoid some shortcomings—notably low efficiency and high toxicity—of previous transgenic methods using retroviral or lentiviral vectors (Shen, 2013). Chinese researchers first applied TALENs and CRISPR/Cas9 to establish site-specific gene mutant RMs and CMs (Liu et al, 2014b; Niu et al, 2014). The myriad studies have demonstrated that using technologies involving TALENs and CRISPR/Cas9, multiple and single genetic mutations can be effectively performed in monkeys (Liu et al, 2014a; Niu et al, 2014).

In addition to the above-mentioned problems, there are still many other key problems with NHP models to resolve, for example, high cost, difficulties regarding how to have a well-defined phenotype characterization, and a genotype-phenotype correlation for NHPs and how to use cutting-edge molecular imaging system to characterize the NHP brain structure and activity for better understanding mental disease.

In summary, NHPs are ideal experimental models for biomedical research. Compared with developed countries in America and Europe, China has advantages in developing NHPs resources. China is a leading producer and a major supplier of NHPs. Although deficiencies in feeding and management may delay China's growth in NHP research and materials, a number of primate animal models for human diseases on infectious diseases, cardiovascular diseases, endocrine diseases, reproductive diseases, neurological diseases, and ophthalmic diseases have been established. Particularly, the site-specific gene mutant RMs and CMs have successfully been born in China. We believe that advances in these studies by using NHP models will undoubtedly further promote the development of China's life sciences and pharmaceutical industry, and enhance China's position as a leader in NHP research.

Acknowledgments: The opinions expressed in this review paper reflect personal views of the authors. Due to the limited space of this paper and/or our ignorance and negligence, we are sorry that we did not include all these related works regarding primate studies in China although we aimed to have a comprehensive review of NHP models of human diseases. We sincerely apologize to all those colleagues whose important work is not cited.

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