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MEETING REPORT

The 3rd Symposium on Animal Models of Primates − The Application of Non-Human Primates to Basic Research and Translational Medicine

In order to understand the fundamental questions of the biology of life and to duplicate the pathogenesis of human diseases, animal models using different experimental animals, such as rodents, *Drosophila*, *Caenorhabditis elegans*, and zebrafish, have been established and used widely for many decades. The controllability of environmental conditions, the high reproducibility, the ease of scale and the comparability of results, as well as the ability to use different standards for ethical protocols, all make an animal model the ideal tool for carrying out studies on human diseases and the development of novel pharmaceuticals and new therapies (Xue et al., 2014). An ideal animal model should reflect the complete spectra of a specific human disease, with similar features on the following key issues: (1) genetic basis; (2) anatomy and physiology; (3) pathological response(s) and underlying mechanism(s); (4) phenotypic endpoints as clinical studies; (5) responsiveness to known drugs with clinical efficacy; and (6) prediction of clinical efficacy (McGonigle and Ruggeri, 2014).

Compared to other experimental animals such as rodents and dog, non-human primates (NHPs) are phylogenetically close to human and have many similarities in terms of their physiology, anatomy, immunology, and neurology, to name a few. All of these similarities make NHPs excellent experimental models for the study of the fundamental biology of the human being, especially in the brain and cognitive sciences, the exploration of disease mechanisms and the development of new drugs, vaccines and diagnostic tools (Zhang et al., 2014). Additionally, the Chinese tree shrew (*Tupaia belangeri chinensis*), has been proposed as an alternative experimental animal to primates, due to its closer evolutionary relationship to primates than rodents, as well as its small body size and short maturity time (Zheng et al., 2014). It has attracted increased attention for modeling human diseases and developing therapies (Xu et al., 2013; Zheng et al., 2014).

China has relatively abundant primate and tree shrew populations, and continues to devote efforts to develop NHPs resources. Currently, China is a leading producer and a major supplier of NHPs on the international market (Zhang et al., 2014). The Kunming Institute of Zoology (KIZ), Chinese Academy of Sciences, has a long history of raising and managing primates and Chinese tree shrews, and has made impressive achievements in primate research during the past decades. The affiliated Kunming Primate Research Center of the KIZ, launched in 2005, was honored as "*China's largest and arguably best primate research facility*" (Hao, 2007). Given the urgent needs in the field of experimental primates and animal models of human diseases, it is essential to establish a specific forum for researchers from home and aboard to share their findings and opinions in primate animal model research and to develop connections between both basic and applied research groups. The KIZ therefore started a specific symposium on Animal Models of Primates from 2012 in Kunming. The series of symposia has fulfilled this goal and was fortunately supported by the National Natural Science Foundation of China (NSFC) and other funding agents.

The 3rd symposium was held on December 4−7, 2014 in Kunming, China (http://amhd2014.csp.escience.cn/dct/page/1). It started with an opening remark by Prof. Yong-Gang Yao, on behalf of the meeting organizers and the KIZ, in which he extended his warm welcome to all participants and guests. He then introduced the background and significance of the symposium and the main achievements of the KIZ on NHP research. Prof. Erdan Dong, the executive director of the Department of Health Sciences, NSFC, summarized the overall development and progress in the research uses of animal models in China. He reviewed the current grants and financial supports in the field of animal models funded by the NSFC (Xue et al., 2013, 2014). By the use of facts and numbers, Prof. Dong demonstrated the gap between Chinese researchers and their international counterparts. Meanwhile, Prof. Dong affirmed that the NSFC will continue to heavily support research into the use of animal models with high originality, groundbreaking influence, and potentially wide usage in the coming five-year term (2016−2020). "'*Good tools are prerequisite to the successful execution of a job', and animal models are undoubtedly the best tools to dissect underpinning of human disease and to promote new drug discovery and new therapeutics*", with this remark, Prof. Dong ended his splendid presentation.

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Twenty six researchers from Columbia University, University of Pennsylvania, Hong Kong University of Science and Technology, Institutes of the Chinese Academy of Sciences (e.g., KIZ, Institute of Genetics and Developmental Biology, Institute of Neuroscience, and Institute of Biophysics), University of Science and Technology of China, China Agricultural University, Wuhan University, Nanjing Medical University, Soochow University, Beijing Normal University, Peking University, Chinese PLA General Hospital, Guangxi Medical University, Chinese Association for Experimental Primate Breeding and Development, Guangdong Landau Biotechnology Co. Ltd., etc. presented their impressive findings about the use of animal models in the study of infectious diseases, metabolic disorders, cancer, cardiovascular diseases, and neuropsychiatric disorders. Specifically, Dr. Neng Gong provided convincing data and interesting videos to show mirror-induced self-directed behaviors in rhesus monkeys after visual-somatosensory training. Their findings, later formally published in *Current Biology* (Chang et al., 2015), provided the first evidence that monkeys could learn to see themselves in the mirror and shed lights on the origin of mirror self-recognition, a hallmark of higher intelligence in monkeys. Another impressive study, as presented by Prof. Xiaojiang Li, showed that the transgenic Parkinson's disease (PD) rhesus monkeys expressing mutant α-synuclein (α-syn A53T) in the monkey brain demonstrated age-dependent non-motor symptoms, including cognitive defects and anxiety phenotype. Their transgenic PD monkeys had the face validity and construct validity of an animal model for the central nervous system, and might be used for testing drugs in the treatment of early PD (Niu et al., 2015). Prof. Wu Li presented their interesting results on the incremental integration of global contours through interactions between visual cortical neurons (Chen et al., 2014), and showed that perceptual training could continuously refine neuronal population codes in the primary visual cortex (Yan et al., 2014). Prof. Xintian Hu made an overview of their NHP animal models of depression (Chu et al., 2014) and early adversity induced by maternal separation (Feng et al., 2011). Prof. Yong-Tang Zheng and Prof. Wen-Zhe Ho brought new advances regarding NHP models of HIV and tuberculosis, respectively. Prof. Gong Chen presented their ambitious thought and attempts to establish a NHP model for *in vivo* glial scar reversing and brain repair – they had a successful try with a mouse model (Guo et al., 2014).

The symposium was lucky enough to have several good presentations on tree shrews, a close relative to primates (Zheng et al., 2014). Prof. Bin Liang had a comprehensive presentation about tree shrew models generated by collaborative teams from the Key Laboratory of Animal Models and Human Disease Mechanisms, Chinese Academy of Sciences, including models of chronic social defeat depression (Wang et al., 2011, 2013), breast cancer (Xia et al., 2014), bacterial infections (Li et al., 2012), non-alcoholic fatty liver disease and HSV-I infection (unpublished data). Also, he showed accumulated data on the basic biology of Chinese tree shrew, in particular for the tree shrew genome database (www.treeshrewdb.org) (Fan et al., 2014). Many of these data have been included in the recently published monograph "*Basic Biology and Disease Models of Tree Shrews*" that was edited by Professors Yong-Tang Zheng, Yong-Gang Yao, and Lin Xu (Zheng et al., 2014). Prof. Jiang-Ning Zhou showed a complete story regarding the molecular basis and regulation of social defeat in tree shrews.

One unique feature of the symposium was to provide a chance to meet leading experts working on other experimental animals such as zebrafish and pig. This fosters an atmosphere of comparative medicine and extends our thoughts beyond NHP and tree shrews. Prof. Zilong Wen had a wide presentation of their efforts on exploring the role of microglia in the nervous system in zebrafish, while Prof. Han Wang discussed the example of their zebrafish model of circadian rhythmicity and uncovered the underpinning of circadian modulation of dopamine levels and dopaminergic neuron development that contributes to attention deficiency and hyperactive behavior (Huang et al., 2015). Based on their own experience and data, Prof. Liangxue Lai detailed the genetic manipulation techniques for generating genetically modified pigs, in particular the use of the cutting-edge technologies such as CRISPR/Cas9-mediated gene-targeting (Zhou et al., 2015). Dr. Zhengquan Yu presented their work on generating a transgenic pig model of autosomal dominant polycystic kidney disease (He et al., 2013).

A good animal model paves the way for advancing our understanding of disease mechanisms and for identifying potential novel targets for disease treatments. Prof. Antonio Iavarone gave us an extensive presentation about the master regulators and drivers of oncogenesis of glioblastoma that they identified in human patients and how they confirmed the function of the regulators and driver mutations using a mouse model. He further extended their study into translation medicine and showed how their results affected the clinical diagnosis of the field by way of example (Di Stefano et al., 2015). Prof. Karl Herrup had a broad presentation about their efforts in characterizing the Cdk5 cyclin-like protein p25 (CDK5R1), which preferentially binds and activates GSK3β and has important implications for the development of neurodegenerative diseases (Chow et al., 2014). Prof. Jiali Li gave an interesting talk regarding the selective loss of 5hmC that links ATM-deficiency to Purkinje cell vulnerability, which shed light on the role of epigenetic regulation in neurodegenerative diseases.

Other presentations at the symposium, which were not detailed in this meeting report due to limited space, showed how the use of animal models can affect the progress in a field of study and assist with better understanding of the human diabetes and cardiovascular diseases.

The symposium also reserved free time for open discussions regarding several key issues: (1) How to develop essential collaborations among researchers, and to share the genetically modified animals and animal models under a mutually benefited agreement? What is the biggest obstacle for doing that? (2) How to unite together and keep our leading position of NHP research in China, giving that we have plenty of primate resources and the recent advance of genetic

modifications (Liu et al., 2014a,b; Niu et al., 2014)? (3) How to translate the research results into pharmaceuticals and clinical application? We believe that with more open discussions on these important issues at the symposium and other conferences with similar topics, we will be able to approach our goal in the coming years, and advance our research on animal models. This series of symposia has given and will continue to provide a timely platform for the appropriate application of different animal models, in particular for the use of NHPs.

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