Neuron
NeuroView

China Brain Project: Basic Neuroscience, Brain Diseases, and Brain-Inspired Computing

Mu-ming Poo,[1,2,*] Jiu-lin Du,[1,2] Nancy Y. Ip,[3] Zhi-Qi Xiong,[1,2] Bo Xu,[2,4] and Tieniu Tan[2,4,*]
[1]Institute of Neuroscience, Chinese Academy of Sciences, 200031 Shanghai, China
[2]CAS Center for Excellence in Brain Science and Intelligence Technology, 200031 Shanghai, China
[3]Division of Life Science and State Key Laboratory of Molecular Neuroscience, The Hong Kong University of Science and Technology, Hong Kong, China
[4]Institute of Automation, Chinese Academy of Sciences, 100190 Beijing, China
*Correspondence: mpoo@ion.ac.cn (M.-m.P.), tnt@nlpr.ia.ac.cn (T.T.)
http://dx.doi.org/10.1016/j.neuron.2016.10.050

The China Brain Project covers both basic research on neural mechanisms underlying cognition and translational research for the diagnosis and intervention of brain diseases as well as for brain-inspired intelligence technology. We discuss some emerging themes, with emphasis on unique aspects.

Introduction

The past few years have witnessed a global awareness of the importance of brain research, as exemplified by large brain projects initiated in Europe, the U.S., and Japan. Discussions among Chinese scientists in many strategic meetings organized by the Ministry of Science and Technology and Natural Science Foundation of China have led to the consensus that understanding the neural basis of human cognition, a universal goal of neuroscience, should form the central pillar of the China Brain Project. Moreover, China should also devote her resources and research capabilities to address immediate societal needs. The escalating societal burden of major brain disorders calls for the development of new preventive, diagnostic, and therapeutic approaches. In the new era of big data, brain-inspired computing methods and systems are essential to achieve stronger artificial intelligence (AI) and to harness the ever-increasing amount of information. These considerations led to the "one body, two wings" scheme of the China Brain Project (Figure 1), in which the basic research on the neural circuit mechanisms underlying cognition provides inputs to and receives feedback from the two applied wings of brain disease diagnosis/intervention and brain-inspired intelligence technology.

The China Brain Project, entitled "Brain Science and Brain-Inspired Intelligence," is formulated as a 15-year plan (2016–2030), with the first five years coincident with China's 13th five-year plan for national social and economic development. As a relatively new research discipline in China, neuroscience has a small community and needs increased government support for building research capacity in nearly all areas. On the other hand, given the current limited capacity, the project also needs to focus on selective areas, particularly those in which Chinese scientists have some advantages and may contribute in a significant way. Some of these areas are discussed in this NeuroView. The key issue at present is how the Project will be managed in line with the new reform in S&T management systems, which is among the top priorities of the present government.

Neural Circuit Mechanisms of Cognition

Understanding human cognitive processes represents an ultimate challenge to the human understanding of nature. It requires not only description of phenomena related to cognition at different levels, from behaviors to neural systems and circuits to cells and molecules, but also mechanistic understanding of the causal linkage among phenomena observed at different levels. Thanks to the rapid progress in brain imaging technologies and in molecular and cell biology, much progress has been made in understanding the brain at the macroscopic and microscopic levels. However, there is an enormous gap in our knowledge at the mesoscopic level. We know very little about how neural circuits are assembled from specific types of neurons in different brain regions and how specific neural circuits perform their signal processing functions during cognitive processes and behaviors. This requires detailed information on the architecture of neural circuits at single-cell resolution and on the spatiotemporal pattern of neuronal activity.

For mesoscopic understanding of the brain, it is imperative to identify all neuronal types, a task begun more than a century ago by Ramon y Cajal, based only on neuronal morphology. Recent developments of single-cell RNA-sequencing methods have accelerated the pace of cell-type identification by classifying neurons based on their distinct protein expression profiles. However, protein expression is neuronal state dependent, and in some cases it may be difficult to distinguish a new cell type from a new state of the same neuronal type. Since neurons of the same type in a given brain region are likely to perform the same circuit function by their distinct input and output connectivity, mapping all local and long-range connections of each neuron ("single-neuron connectome") becomes essential for defining the neuronal type. Here, relatively specific molecular markers delineated by single-cell RNA-sequencing analysis could be used reiteratively with single-neuron connectome analysis to eventually define a neuron type based on both the unique pattern of input-output connectivity and molecular markers. Once the cell type is defined, specific molecular probes expressed in neurons could be used to monitor and perturb their activity, in order to dissect neural circuit mechanisms underlying brain cognition and behaviors.

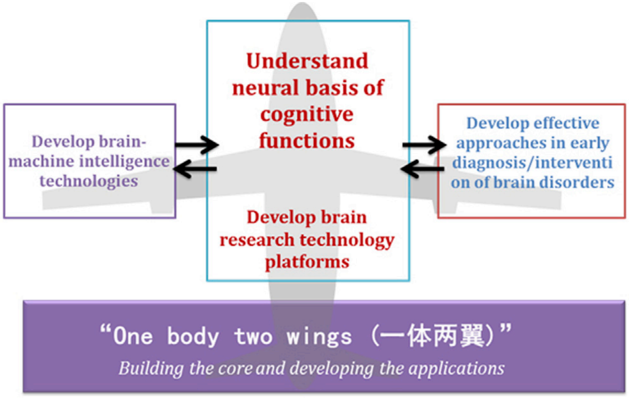

Figure 1. The Framework of China Brain Project “Brain Science and Brain-Inspired Intelligence,” 2016–2030

Optimists among us may expect within the next two decades the completion of mesoscopic mapping of neural circuits and their activity patterns, and perhaps even the underlying logic and mechanisms, of cognitive processes in animal models such as *Drosophila*, zebrafish, and rodents. Basic cognition of the outside world, including sensory perception, sensorimotor transformation, categorization, concept formation, and decision-making can be examined in these small animal models. These studies could provide a basis for understanding of conserved cognitive mechanisms at the mesoscopic level. Cognition of self and non-self, empathy, and theory of mind, on the other hand, are likely to be present only in non-human primates (NHPs). These high-level cognitive functions are a prelude to the evolution of language, a unique cognitive ability of humans. The explosive growth of the neocortex in primates has endowed new connectivity that could define many new neuronal types and circuits that are absent in other animal models. Many technologies developed in rodent studies are now applicable to NHPs (Stauffer et al., 2016). In our opinion, given the rich resources of NHPs in China, the China Brain Project should include a substantial NHP component on the mesoscopic circuit analysis of the macaque brain, in parallel with other programs that focus on non-primate animal models. The NHP project is likely to require a much longer duration than that for rodent projects, but it is essential for brain science to reach its ultimate goal.

In line with the main focus of Japan’s Brain/MIND project on marmosets, the China Brain Project could make a significant contribution in studying cognition in macaque monkeys. Mesoscopic structural and functional mapping of macaque neural circuits would require cell-type identification through single-cell RNA-seq and single-neuron connectome analysis, described above. There is also an urgency in studying circuit mechanisms underlying cognitive processes in NHPs, because the relationship between mesoscopic and macroscopic imaging found in NHPs will greatly facilitate the interpretation of human brain imaging data at the neural circuit level, the development of diagnostic/therapeutic approaches for human brain disorders, and the design of new architecture for artificial neural networks and multi-purpose intelligent devices.

Early Diagnosis and Intervention of Brain Disorders

It is estimated that about one-fifth of China’s population of 1.3 billion currently suffers from chronic neuropsychiatric or neurodegenerative diseases (Phillips et al., 2009; Chan et al., 2013). The China Brain Project aims to study the pathogenic mechanisms and to develop effective diagnostic and therapeutic approaches for brain disorders that are developmental (e.g., autism and mental retardation), neuropsychiatric (e.g., depression and addiction), and neurodegenerative (e.g., Alzheimer’s disease [AD] and Parkinson’s disease [PD]). The urgency in reducing the escalating societal burden associated with these disorders and the ineffectiveness of current therapies call for the early diagnosis at pre-symptomatic and prodromal stages, so that early intervention may be introduced to halt or delay the disease progression.

Early diagnosis will benefit from research that unravels disease pathophysiology at the molecular, cellular, and circuit levels. Omics-based approaches will facilitate identification of genetic factors, cell-type-specific epigenetic factors, protein expression and modification, and lipid composition and metabolism. High-throughput analysis of large population samples will help to identify disease-specific prognostic markers and shed light on the interaction between genetic and environmental factors. For developmental disorders, it is critical to determine the mechanisms underlying the impairment of neurogenesis, neuronal migration and differentiation, synapse formation and plasticity, and neural circuit development. Patient-derived induced pluripotent stem cells (iPSCs) can be used to develop in vitro models (e.g., 3D brain cultures, organoids) that replicate human conditions, to verify genetic risk factors as well as decipher their specific cellular disease phenotypes. Brain imaging studies on patients with disease symptoms will help to identify structural and functional abnormalities of various brain areas. Gene-edited NHP models of brain diseases, based on identified molecular targets, will provide further information for understanding the pathogenesis mechanisms and for developing pharmacological and physiological intervention approaches. Early pharmacological intervention of disease progression, particularly for neurodegenerative disorders such as AD, is a promising front of future drug development, as suggested by the recent progress associated with the clinical trials using antibody therapy of prodromal or mild AD (Sevigny et al., 2016).

Given the fact that most brain diseases show overlapping symptoms due to common neural circuit impairment, quantitative assay of specific brain functions will offer valuable information for identifying high-risk populations for early intervention of specific brain functions. Physiological intervention using extensive training protocols aiming at enhancing specific brain functions has shown promise for preventing a number of neurological and psychiatric disorders. The use of physical stimulation, involving tools such as transcranial magnetic stimulation and transcranial direct current stimulation, has attracted much attention for therapeutic treatments of brain disorders, but the use of these tools suffers from the lack of specificity and physiologically sound basis. Identification of specific neural circuits underlying various dysfunctions and the development of spatially and temporally more precise stimulation methods will facilitate neuromodulatory actions that prevent the deterioration of specific circuit functions.

Development of early diagnostic and intervention approaches requires collection of longitudinal data from large populations of healthy and high-risk subjects. This is possible only through well-orchestrated efforts among scientists, clinicians, and public health organizations. China has the world's largest patient populations for nearly all major brain disorders and urgently needs early diagnosis and intervention. With increasing living standards, continuing improvement of public health systems, strong government commitment for adequate medical care for all citizens, and the tradition of social mobilization, the China Brain Project is well posed to organize large-scale programs aiming at effective early diagnosis and intervention approaches. This includes the establishment of long-term brain health records for large populations, incorporating quantitative brain function tests as part of the regular health examination, and national platforms for brain imaging database, blood-based biobank, and national repository of healthy and diseased brains. The advantage of large patient populations for brain disease studies will become apparent only when the capabilities of many research centers are integrated with standardized data collection and processing and mechanisms for data-sharing and credit allocation are well established.

Input from Chinese Medicine

The complexity of pathogenic mechanisms underlying neuropsychiatric and neurodegenerative disorders has led to the lack of progress in developing effective drugs over the past decades. It has been suggested that it may be more effective to target these diseases with multi-target rather than single-target drugs. The successful practice of centuries-old Chinese medicine (CM) in treating a wide range of ailments is well documented, although the underlying mechanism is largely unknown. As multicomponent drugs, CM formulas are likely to exhibit therapeutic effects by acting on multiple effectors, thus potentially a treasure trove of neuro-drugs. However, the use of CM in modern medical practice has been greatly hindered by its dependence on cumulative empirical experience rather than evidence-based studies, the difficulty in replicating dosages and composition of poorly standardized mixtures of herb extracts in many CM-based medicines, and the lack of precise information on therapeutic effects. There are also very few well-designed clinical trials to provide proof of efficacy, or safety studies to ensure the medicines meet the same regulatory standards that are required for pharmaceuticals.

Efforts to lend a scientific basis to CM practice include systematic investigations in areas such as pharmacognosy, plant chemistry, and pharmacology to amass a vast collection of information on different medicinal herbs and the development of critical rationale for their applications (Qiu, 2015). A more concerted effort is also needed to establish clinical evidence of therapeutic effects of various herb formulas, and many researchers are now isolating active ingredients from medicinal herbs, from crude fractions down to single compounds (Fan et al., 2006). Natural product libraries of these isolated compounds have also been developed to easily screen for molecules with specific biological activities, including those in the nervous system, with identified compounds undergoing rigorous pre-clinical development similar to a pharmaceutical lead candidate. Potential neuro-drug leads for AD have recently been identified using this approach (Fu et al., 2014).

Technological advances are now facilitating our understanding of how CM herbs exert their actions. For instance, gene transcriptional analysis can be used to characterize the mechanisms of action of an herb extract, compound, or formulation, so as to measure their effects at molecular, cellular, and physiological levels. Collectively pooling this information to develop a connectivity map and scanning against molecular signatures of different disease states can then facilitate identification of specific mechanisms of action and physiological processes of active components (Lamb et al., 2006). Other innovative approaches to leverage the clinical potential of CM include mathematical models and algorithms to devise the most optimal mixtures of different CM ingredients. Based on a closed-loop feedback control process, the vast data on CM herbs can be harnessed in an intelligent manner to greatly reduce expensive and labor-intensive assays, while increasing the probability of identifying effective synergistic drug combinations (Nowak-Sliwinska et al., 2016). Improvements in clinical design, quality control, and safety studies will further enable modern medicine to tap the elusive benefits of CM and unleash their intrinsic value in clinical drug therapy. Through organized national efforts, the China Brain Project could leverage this unique resource for neuro-drug discovery and development.

Non-human Primate Research

Being phylogenetically most proximal to humans, NHPs are excellent animal models for studying human cognitive functions and for exploring pathogenesis mechanisms and therapeutic approaches for brain diseases. There is increasing interest in the use of NHPs among Chinese neuroscientists, and new NHP research facilities are being established in many research institutions (Cyranoski, 2016). For example, the Kunming Institute of Zoology of Chinese Academy of Sciences (CAS), which already has a large colony of macaque monkeys for research purposes, is in the process of further expansion into the National Primate Resource Center, potentially the largest NHP research resource in China. Yunnan Key Laboratory of Primate Biomedical Research in Kunming now houses a collection of gene-edited monkeys that may serve as models of Duchenne muscular dystrophy, autism, and PD. A NHP facility maintained by Chinese Academy of Medical Sciences in Kunming for vaccine development is now shifting its interest toward developing NHP models for brain diseases. Finally, the Institute of Neuroscience of Chinese Academy of Sciences in Shanghai has established the largest NHP research facility in East China for both macaque and marmoset monkeys, together with ten research laboratories working on reproductive biology, gene-edited models, systems neurophysiology, and cognitive behaviors of NHPs.

Surgical intervention and chemical induction have been used in the past to generate NHP models for brain disorders such as drug addiction, spinal cord injury, epilepsy, and PD and AD (Zhang et al., 2014). In recent years, transgenic and gene-editing approaches have begun to be used for developing NHP models for those diseases with prominent genetic causes, including Huntington's disease, PD, Duchenne muscular dystrophy, and autism spectrum disorders (Chen et al., 2016; Liu et al., 2016a). Virus-mediated gene delivery was the main approach for generating transgenic monkeys expressing *a-Synuclein* and *MeCP2*. New gene-editing technologies have been used to generate gene-edited NHP models (Chen et al., 2016): TALEN technique was used to knock in human-derived mutation in *MeCP2* for modeling Rett syndrome caused by MeCP2 deficiency, and CRISPR-Cas9 approach was first achieved in deleting a non-neuronal gene, *Dystrophin*, in macaques, and the same method also achieved double-knockout of *Ppar-*γ and *Rag1* in one-cell-stage macaque embryos. Notably, the *p53* biallelic genes were knocked out simultaneously, resulting in the generation of homozygous mutant monkeys (Chen et al., 2016). The long duration of sexual maturation and gestation in macaques imposes a significant barrier to the development of genetically modified NHP models that require germline transmission, although the duration for generating F1 in macaques (5–6 years) could now be shortened to 2.5 years with testis xenografting technique that accelerated sperm maturation (Liu et al., 2016a, 2016b).

Rich resources of NHPs and strong interest in using NHPs do not imply that ethical standards for NHP experimentation could be more relaxed in China (Zhang et al., 2014). The China Brain Project aims to establish nationwide ethical regulations for NHP experimentation that are compatible with international standards and to promote public dissemination of the awareness that NHP research is indispensable for developing effective therapies for human diseases, particularly brain disorders, and for advancing our knowledge of the evolution and function of the human brain. Given the declining NHP research in the Europe and the U.S., national brain projects in Asian countries also shoulder the responsibility of sustaining the tradition of NHP research in neuroscience and training the new generation of primate neurobiologists.

Brain-Inspired Computation

Neuroscience has focused on detailed studies of neural coding, dynamics, and circuits, while machine learning tends to pursue brute-force optimization of a cost function, often using simple and relatively uniform initial architecture (Marblestone et al., 2016). Recent progress in AI and deep learning in particular has shown its capability for handling cognitive tasks in restricted specific fields. Despite the fact that AI systems (such as AlphaGo) outperform human beings in certain tasks (Silver et al., 2016), they still suffer from the lack of generalizability and the ability to transfer learned knowledge from one task (domain) to another. Also, labor-intensive labeled data are needed to tune the huge number of parameters of such deep learning models. Another key problem is the high computational (energy) cost and high throughput data for training and running these AI systems. The human brain is currently the only truly general intelligent system in nature, capable of coping with different cognitive functions with extremely low energy consumption. Learning from information processing mechanisms of the brain is clearly a promising way forward in building stronger and more general machine intelligence.

Although we are far from completely understanding how the brain really works, current findings from neuroscience could potentially impact AI research from several perspectives. From the structure perspective, the morphology of different types of neurons, the stabilization and pruning of connections during development and learning, the layered architecture of the neocortex, feedforward and feedback connections within and among brain regions, and the motifs of brain building blocks at multiple levels offer new insights into the architectural design of artificial neural networks. From the mechanism perspective, spike information encoding and decoding, different types of spiking neurons with distinct functions, multiple synaptic types and plasticity mechanisms, rules for conversion from short- to long-term memories, and integration of information processing at different levels (neurons, micro-circuits, brain regions) bring potential operational principles for designing efficient computational models and algorithms for general AI. From the behavior perspective, observations and analysis on how different cognitive functions are coordinated and integrated by the brain will bring inspiration and evaluation criteria for intelligent systems that are brain-like in their cognitive performance.

The brain was shaped by evolution into a highly energy efficient system. Its structure and underlying mechanisms may provide inspiration for the design of future computing infrastructures. Unlike traditional computation, neural systems process information in a way of total binding of computing and storage. Recent efforts in designing neuromorphic chips have focused on creating brain-inspired chips that are highly energy efficient (Tuma et al., 2016), by implementing a few microscopic-level principles of neural circuits, such as nonlinear neuronal properties of integrate-and-fire, spike timing-dependent plasticity (STDP), and integrated computation and storage. Higher-level architecture could also be considered in the future as building blocks for chips to simulate organized structures of cortical columns, brain regions, and neural pathways that connect multiple brain regions, in order to achieve efficiency and high throughput in information processing.

The China Brain Project aims at better understanding of mechanisms and principles of the brain at multiple levels and is expected to promote deep and close collaboration between neuroscientists and AI researchers. Cognitive computational models and brain-inspired chips will be the primary focus of the intelligence wing. At the level of computational models, artificial neural network algorithms with more biological plausible learning mechanism will be explored. At the network architectural level, typical human cognitive behavior will be modeled through introduction of brain-like domains and sub-domains within the network that are coordinated, integrated, and modifiable through learning. The goal is to simulate in principle the mechanisms and architecture of the brain at multiple levels to meet the grand challenge to making a general AI that is capable of multitasking, learning, and self-adapting.

Machines with Human Intelligence

Achievements of AI in past decades, including recent deep learning models, have been inspired in part by neuroscience. Recent development mainly depends on single optimization principles of objectives, such as minimizing classification errors. This led to the formation of rich internal representations and powerful algorithmic capabilities in multilayer and recurrent networks (LeCun et al., 2015). In the past five years, deep learning has enjoyed great success in solving a variety of problems such as speech recognition, image recognition and classification, and natural language processing. In speech recognition, an accuracy as high as 95% has been reported by IBM and Microsoft in human telephone call conversation tasks, greatly exceeding the level that had plateaued for a decade. In computer vision, the deep learning network also surpasses human performance in ImageNet classification challenge in locating and recognizing hundreds kinds of objects. In natural langue processing, an LSTM-based sequence-to-sequence model for machine translation almost reaches the human interpreter level. Machines could even annotate an image using natural language, after being trained with millions of image-text pairs collected from the internet. In all the above examples, structured architectures are used, including dedicated systems for attention, recursion, and various forms of short- and long-term memory storage.

However, models driven by massive training data meet great challenges for more open and ill-defined tasks like natural language understanding, human dialog system, general visual information retrieval, and robotic adaptation to complex environment. Aligning to brain mechanisms, AI systems are expected to exhibit stronger intelligence with less training data or even with unsupervised learning. Furthermore, they are expected to process and integrate multimodal information and handle multiple tasks in parallel. We have witnessed many new types of networks with more dedicated object functions, for example varied across layers and over time, to handle these challenges. The new advance in adversarial networks, where the cost function is provided by another network, allows gradient-based training of generative models (Goodfellow et al., 2014). Such a heterogeneously optimized system, enabled by a series of interacting cost functions, makes the learning data-efficient and precisely targeted to the need of the intelligence, and it is one of the future directions for machine intelligence.

Another essential issue in developing machine intelligence is to build an AI platform that could interact with human and local environment efficiently, in which both human and machine are in the loop of problem solving. Cognitive robotics could serve as an integrating platform of this kind to integrate many efforts of brain-inspired research. Traditional robotics research focuses on control theory and mathematical optimizations. The models work well in structured environment and restricted tasks (e.g., robotic arm in factories), but cannot navigate correctly even in not-so-complex environments. Substantial improvement has been made in robotics for the coordination and integration of multi-sensory inputs and execution mechanisms with more information and flexibility. But for cognitive robotics, much more could be learned from the network structure, operating principles, and circuit mechanisms of sensorimotor transformation in the brain, including multi-sensory integration, decision-making, motor planning, and motor coordination and execution, in a manner that the operation could be learned and underlying circuits self-modified by experience.

The China Brain Project will focus its efforts on developing cognitive robotics as a platform for integrating brain-inspired computational models and devices. The goal is to build intelligent robots that are highly interactive with humans and properly reactive in uncertain environments, with the skills for solving various problems that can grow through interactive learning, and the ability to transfer and generalize knowledge acquired from different tasks—even to share learned knowledge with other robots. The interface between human and machine is essential; the robot needs not only to understand what the human means and to respond smartly, but also to learn to understand the human intention and the way the human makes decisions. Thus, a useful milestone for cognitive robotics is to build a robot that acquires behaviorally equivalent capability of empathy and theory of mind, a cognitive hallmark of humans and a few primate species.

Concluding Remarks

Future breakthroughs in basic and applied neuroscience depend upon not only fundamental discoveries and technological development in individual laboratories, but also collaborative efforts by large teams of researchers from diverse disciplines. As exemplified by recent advances in the frontier of physics and astronomy, the key to success often lies in the effective organization of the team work, which calls for consensus among the participants for a framework of equitable sharing of duties and credits. This is particularly important for team work that requires individual scientists to devote their major research efforts and resources into the project. Furthermore, the weights our research institutions place on collaborative work versus independent accomplishment in the evaluation of a scientist's achievements are becoming increasingly critical, especially for young scientists in the process of establishing their own research careers. In biological sciences, our institutions have yet to adopt a system of evaluation, e.g., for tenure review, that is conducive to team work.

Complete understanding of the structure and function of the human brain is an attractive but remote goal of neuroscience. However, the limited understanding of the brain that neuroscience has achieved is already useful for addressing some urgent problems our society is facing. For example, identification of early molecular or functional markers for AD could be accomplished prior to our full understanding of the pathogenesis of AD. The China Brain Project aspires to achieve a balance between basic and applied neuroscience, in which some research scientists are capable of pursuing their interest in exploring the secrets of the brain, while others may apply what we know already for preventing and curing brain disorders and for developing brain-inspired intelligence technology.

ABOUT THE AUTHORS

Mu-ming Poo is the Director of Institute of Neuroscience (ION), Chinese Academy of Sciences, and Director of CAS Center for Excellence in Brain Science and Intelligence Technology (CEBSIT). Julin Du is an Assistant Director of ION and Associate Director of CEBSIT. Zhi-Qi Xiong is an Assistant Director of ION and Head of ION's Division of Brain Disease Mechanisms. Nancy Y. Ip is the Director of State Key Laboratory of Molecular Neuroscience and Vice-President for Research and Graduate Studies of the Hong Kong University of Science and Technology. Bo Xu is the Director of Institute of Automation, Chinese Academy of Sciences, and Vice Director of SEBSIT. Tieniu Tan is the Chief Scientist of CEBSIT and Vice President of Chinese Academy of Sciences.

REFERENCES

Chan, K.Y., Wang, W., Wu, J.J., Liu, L., Theodoratou, E., Car, J., Middleton, L., Russ, T.C., Deary, I.J., Campbell, H., et al.; Global Health Epidemiology Reference Group (GHERG) (2013). Lancet *381*, 2016–2023.

Chen, Y., Niu, Y., and Ji, W. (2016). J. Intern. Med. *280*, 246–251.

Cyranoski, D. (2016). Nature *532*, 300–302.

Fan, T.P., Yeh, J.C., Leung, K.W., Yue, P.Y., and Wong, R.N. (2006). Trends Pharmacol. Sci. *27*, 297–309.

Fu, A.K., Hung, K.W., Huang, H., Gu, S., Shen, Y., Cheng, E.Y., Ip, F.C., Huang, X., Fu, W.Y., and Ip, N.Y. (2014). Proc. Natl. Acad. Sci. USA *111*, 9959–9964.

Goodfellow, I.J., Pouget-Abadie, J., Mirza, M., Xu, B., Warde-Farley, D., Ozair, S., Courville, A., and Bengio, Y. (2014). arXiv, arXiv:1406.2661, http://arxiv.org/abs/1406.2661.

Lamb, J., Crawford, E.D., Peck, D., Modell, J.W., Blat, I.C., Wrobel, M.J., Lerner, J., Brunet, J.P., Subramanian, A., Ross, K.N., et al. (2006). Science *313*, 1929–1935.

LeCun, Y., Bengio, Y., and Hinton, G. (2015). Nature *521*, 436–444.

Liu, Z., Li, X., Zhang, J.T., Cai, Y.J., Cheng, T.L., Cheng, C., Wang, Y., Zhang, C.C., Nie, Y.H., Chen, Z.F., et al. (2016a). Nature *530*, 98–102.

Liu, Z., Nie, Y.H., Zhang, C.C., Cai, Y.J., Wang, Y., Lu, H.P., Li, Y.Z., Cheng, C., Qiu, Z.L., and Sun, Q. (2016b). Cell Res. *26*, 139–142.

Marblestone, A., Wayne, G., and Kording, K. (2016). arXiv, arXiv:1606.03813v1, http://arxiv.org/abs/1606.03813v1.

Nowak-Sliwinska, P., Weiss, A., Ding, X., Dyson, P.J., van den Bergh, H., Griffioen, A.W., and Ho, C.M. (2016). Nat. Protoc. *11*, 302–315.

Phillips, M.R., Zhang, J., Shi, Q., Song, Z., Ding, Z., Pang, S., Li, X., Zhang, Y., and Wang, Z. (2009). Lancet *373*, 2041–2053.

Qiu, J. (2015). Natl. Sci. Rev. *2*, 377–380.

Sevigny, J., Chiao, P., Bussière, T., Weinreb, P.H., Williams, L., Maier, M., Dunstan, R., Salloway, S., Chen, T., Ling, Y., et al. (2016). Nature *537*, 50–56.

Silver, D., Huang, A., Maddison, C.J., Guez, A., Sifre, L., van den Driessche, G., Schrittwieser, J., Antonoglou, I., Panneershelvam, V., Lanctot, M., et al. (2016). Nature *529*, 484–489.

Stauffer, W.R., Lak, A., Yang, A., Borel, M., Paulsen, O., Boyden, E.S., and Schultz, W. (2016). Cell *166*, 1564–1571.e6.

Tuma, T., Pantazi, A., Le Gallo, M., Sebastian, A., and Eleftheriou, E. (2016). Nat. Nanotechnol. *11*, 693–699.

Zhang, X.L., Pang, W., Hu, X.T., Li, J.L., Yao, Y.G., and Zheng, Y.T. (2014). Zool. Res. *35*, 447–464.