转化医学研究（电子版）2011，1（2）：8－16
Translational Medicine Research（Electronic Edition），2011，1（2）：8－16

Monograph



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Editor's note: *The aim of recommending this paper to our readers is to address the idea, i. e., translational research requires more increased attention of clinical application. Based on patient-driven research process, Tiantan hospital supports translational research at three steps in the development and perfection of data bases and multi-platforms for integrating of basic and clinical researches and drug innovation, thereby laying a foundation for understanding cerebrovascular events and exploring new drugs.*

Tiantan stroke clinical and translational research in practice: advancing from theory

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Stroke is the number one killer in China[1,2], despite the doubling of healthcare costs. Also, research in the prevention and treatment of cerebrovascular disease has yet to yield satisfactory results. For many years, research in cerebrovascular disease lacked systematic starting points and uninterrupted study. In addition, there is a lack of prevention and treatment tools, especially in research, development, and translational implementation of evidence-based guidelines. Research on the mechanisms and methods of prevention for many diseases has not yet lead to reliable conclusions and is far from satisfying China's urgent need for development of disease prevention. The integration of basic science cerebrovascular research, drug development, and clinical practice to solve critical problems in medicine is an effective method in answering fundamental questions. Patient-centered research in clinical practice is the fundamental goal of Tiantan Hospital translational and clinical research in stroke [3-5].

1 Research rationale

Tiantan Hospital cerebrovascular clinical and translational research projects are aimed to become the frontier of 21st century life science and biotechnology innovations. Based on China's "115" project for supporting technological development, critical emphasis is placed on the development of novel pharmacotherapies. The research and development goals of the Beijing Ministry of Technology include using key research laboratories in Beijing for translational cerebrovascular research to utilize problems from clinical practice and re- form the existing organizational model to operate on a

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translational research model. In supported institutions, there is complete integration of research personnel, large scientific facilities and an ample number of instruments, scientific data, and samples from clinical cases. Through effective deployment and sharing of resources such as pathophysiology, epidemiology, genomics, proteomics, molecular biology, animal models, and medical imaging, the study of stroke etiology, diagnostics and therapeutics may become highly systematic and efficient. At the same time, community-based national cerebrovascular epidemiology and genetic epidemiology monitoring networks were established, based on the storage of clinical data and samples, encompassing cases of various etiologic, genomic, and pharmacogenetics categories. Based on a system of drug discovery, screening, preclinical and clinical testing, and testing/evaluation with medical imaging and research laboratories, the goal is to analyze basic cerebrovascular research data and close the gap between basic and clinical research to effectively combine research to form patient-oriented therapy. This would ultimately satisfy the goals of Beijing's and China's innovative basic and translational research programs on stroke.

2 Research road map

The path for translation research in cerebrovascular medicine was divided into three phases (Fig. 1).

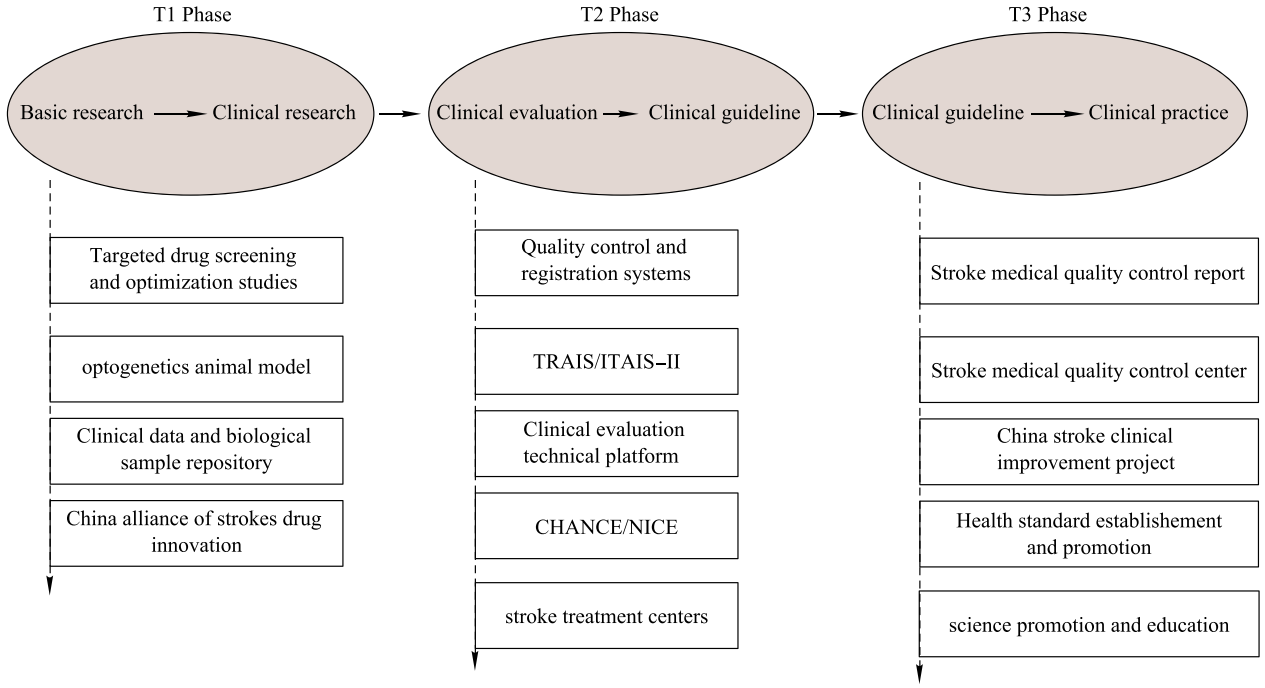

Fig. 1 Clinical and translational stages for stroke studies

T1 phase: Based on questions raised from clinical practice and starting with problems demanding prompt solutions in cerebrovascular diagnosis, prevention, treatment, recovery and other clinical fields, this phase aimed to perform multidisciplinary integration based on methods and theories from basic science research, basic research, pre-clinical, and preliminary clinical evaluation and verification.

T2 phase: In targeting diagnostic and treatment measures evaluated during the pre-clinical and early clinical phases, this phase aimed to perform large-scale, systematic, and standardized clinical evaluation and verification. Through systematic evaluation, evidence-based clinical guidelines and recommendations were developed. In addition, this project also included standardized clinical molecular typing and large-scale individualized biotherapeutic technology.

T3 phase: Evidence-based clinical guidelines for contributing to clinical practice were developed. Evidence-based medicine guidelines were implemented through disease management, performance evaluation, quality improvement, and other modern management techniques for appropriate applications. Through large-scale promotion of evidence evaluation regarding the tangible effects, benefits, and risks, this project aimed at introducing new clinical questions that could be used in the T1 phase.

Through the implementation of this project, results have been obtained and progress has been made in different stages of our translational tasks, as shown in the following areas:

T1 phase: Beginning from clinical needs in stroke, and based on the translation of applications from the laboratory to the human body, targeted drug screening and

optimization studies were performed. As remarkable progress has been achieved within the field of transmembrane receptor research, these research studies have set a firm foundation for related targeted drug screening studies. In addition, this project has also established the world's first optogenetics cerebrovascular animal model, which was published in Gene Discovery for Disease Models[6].

Beijing's top-ten disease technical publication "Stroke Clinical Data and Biological Sample Repository" was constructed as an "information platform" and "samples gallery". The "information platform" is a collection of patient information, follow-up, and research information collected during this study. The "samples gallery" is a centralized clinical research storage database of samples collected from patients with stroke. The samples include, for example, serum, cells, genetic material, and tissue. These measures provide a large scale of high-quality original innovation resources for potentially improving public health, controlling serious illnesses, and promoting development in the pharmaceutical industry. At the same time, the construction of the libraries will become a national resource that is important for the development of a medical resource system, and will play an essential role in the advancement of translational medicine.

In June of 2010, the China Alliance of Strokes Drug Innovation was formed for the purpose of constructing an exchange platform between industry and academics for completing drug synthesis, extraction, clinical or industry-supported pre-clinical research and phases I-III of clinical trials.

T2 phase: The Ministries of Science and Technology, Ministry of Health, and Beijing Municipal Science and Technology Commission are responsible for leading the cerebrovascular research project and have established more than 130 research centers nationwide with quality control and registration systems for early treatment of acute stroke. The project performs the evaluation of safety and efficacy of thrombolytic therapy within a 3 h window for general Chinese stroke patients under real medical service (TRAIS). It also explores the safety and efficacy of thrombolytic therapy with multi-modal CT/MRI imaging within the 3~6 h window (ITAIS-II). This project developed and optimized treatment plans, clinical practice routines, and diagnostic criteria of thrombolytic therapy for acute ischemic stroke, which were subsequently approved by stroke experts in China. In addition, within the realm of China's feasible clinical environment, imaging guidelines and operating procedures for managing acute ischemic stroke were also developed. Several levels of medical institutions were formed to promote standard thrombolytic treatment and individualized thrombolytic therapy. Lastly, a series of acute stroke management was developed to improve clinical care and the series included stroke rating software, a CD-ROM training program for clinical stroke, acute stroke thrombolysis green channel process management software, and other toolboxes for managing thrombolysis.

The "Notable innovative drug development" of novel cerebrovascular drug clinical evaluation technical platform integrates useful resources and is in accordance with GCP principles. Based on phases I-IV of a clinical study, this project longitudinally established technical support platforms such as clinical consultation, policy and regulation consultation, clinical trial implementation, and analysis and evaluation of clinical results. Other horizontal implementations include technological innovations related to clinical evaluations for characterizing strokes including centralized stroke imaging interpretation, centralized electronic follow-up, electronic records and case report forms (e-CRF), a clinical research coordinator network, and a cerebral angiography core laboratory. These horizontal and vertical approaches complement one another to create a platform for international exchange between academic and research organizations focusing on cerebrovascular research. Based upon this platform, The Dual Antithrombotic Therapy TIA/Minor Stroke Randomized Controlled Trial (CHANCE) study was initiated and has enrolled 5100 patients, filling the void in China's research involving evidence-based treatment of TIA/Minor Stroke[7]. In addition, the phase IV Nimodipine for Prevention and Treatment of Mild Cognitive Impairment after Acute Ischemic Stroke: Evaluation of Safety and Efficacy (NICE) trial has been initiated.

In addition, stroke treatment centers are comprised of integrated neurosurgery, neurology, neuroimaging, interventional neurology, neuroepidemiology, neurogenetics, and drug research and development elements for confronting problems in strokes based on basic and clinical research. In these centers, teams perform stroke prevention and management, bypass surgery for ischemic stroke and ischemic stroke, acute endovascular surgery, minimally-invasive techniques for cerebral aneurysms and diagnostic techniques for early acute stroke imaging, which altogether may garner a reputation at home and abroad.

T3 phase: Based on the National Stroke Database (CNSR)[8], the publication "Strokes 2010, Chinese Medical Quality Control Report"[9] found shortcomings in the clinical practice of stroke care. These included the hospital care service quality key performance indicator (KPI) for patients with ischemic stroke, particularly in the prevention of deep venous thrombosis and anticoagu-

lation in atrial fibrillation. A significant gap exists in these areas between China and the U. S. This provides strong evidence and support for the healthcare decisions that have been made by the government. Based on the above results, China has established the Ministry of Health for Stroke Medical Quality Control Center, which contains over 300 network monitoring sites throughout the country, covering different provinces and cities. Its core responsibilities are to monitor, improve, train, and control the quality of care for stroke and oversee international exchange. For the above reasons, the "China Golden Bridge Stroke Clinical Improvement Project" also received major support from the national "125" project. Its purpose is to correctly apply clinical guidelines to clinical practices at the appropriate time, using evidence-based medical guidelines that were demonstrated through disease management, performance evaluation, quality improvement and other modern management methods. On the basis of monitoring, this project will continue to improve the quality of stroke medical care, establish medical services standards and a quality improvement system, and stroke centers and corresponding certification standards.

This project also set up a nationwide network for cerebrovascular research encompassing hundreds of medical institutions with trained clinical researchers focusing on stroke. It supported the Ministry of Health and Disease Control in the establishment, promotion and training of "China Stroke Prevention and Treatment Guidelines" while simultaneously establishing health standards for the Ministry of Health in "Ischemic Stroke Standards of Care", "Adult Diagnostic Criteria for Spontaneous Intracerebral Hemorrhage", and consensus of more than ten other medical experts. The China Acute Ischemic Stroke Etiology and Pathophysiology Categorization Standard (CISS) have been established and have been promoted nationwide[10]. Subsequent developments include a series of tools valuable for improving acute stroke care, such as the clinical stroke scale (NIHSS and mRS score) standard assessment CD-ROM, standardized stroke training CD-ROM, acute stroke thrombolysis green channel electronic medical records and electronic workflow management software, the emergency thrombolysis toolbox, Chinese Stroke Network (www. chinastroke. com) and Percussion Hammer Forum (www. rhammer. com), and Chinese Stroke Thrombolysis registry (www. timschina. net). In the area of science promotion and education, the National Stroke Prevention and Treatment Office collaborated with other units in the creation of four educational films for nationwide release and also prepared three popular science books distributed throughout hospitals in the country.

3 Social benefits

The translational medical research and clinical project at the Tiantan stroke center will integrate laboratory and clinical resources, accelerating the transformation of stroke-related research from basic research to the patient in clinical settings, with the goal of reducing the mortality and medical burden caused by stroke. This project aims to build a complete database of China's largest platform of stroke to lay the foundation for comprehensive study and follow-up research, to provide a basis for China to develop health policy, and ultimately provide data to improve the quality of life for patients with stroke through reductions in mortality and morbidity. For instance, the monitoring of the thrombolytic therapy registry would be effective in promoting the standardization and prevalence of thrombolytic therapy, and may extend the benefit to thousands of people every year. The founding of the "China Alliance of Strokes Drugs Innovation", integrating advantageous resources, building a platform bridging industry and academia, reviewing the direction of innovation in drug development, researching innovative drugs, formulating new treatments, promoting the combination of studies, carrying out research and production in the field of drug discovery for stroke, will help China's stroke-related pharmaceutical industry achieve healthier and rapider development, and become a powerful stimulus in China's economy. We should simultaneously educate and train stroke translational medical specialists, promote the development and popularization of translational medicine in our study of stroke, allowing more achievements in the stroke studies to be used in clinical practice at a faster pace, so that patients with stroke will truly benefit from scientific research.

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