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View and Perspective



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Editor's note: *Translational medicine is a new field of biomedicine. The goal of pursuing translational medicine is the conversion of scientific discovery into health improvement, although it is differently defined nowadays. Here the author recounts the emergence and development of translational medicine and relates its impacts on China's medical sciences and health service concisely and comprehensively. Furthermore, how to develop translational medicine in China is suggested. With the desire for starting an upsurge of discussing translational research and promoting China's translational medicine, we recommend this article to our readers.*

Priority addressed for the translational medicine in China

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The concept of translational medicine originated in the United States (US)[1], and it has recently become a "hot topic" in China. Areas of controversy in both countries typically involve the definition, significance, and developmental direction of translational medicine. For its current status between China and the US, the clearest discrepancies are mainly in the areas of organizational behavior and the setting of priorities. In the US, the leading role of government is dominant, directly focusing on the reform and renovation of industrial rules. In China, the collective appeals from clinical and fundamental research institutions are the major influence; however, reforms are still needed in the areas of regulation of scientific research, the registration system, and mechanisms for taking new drugs and novel technologies from the bench to the market. The challenge we face is to achieve the "circulation model" of translational medicine, i. e. Lab-Clinics-Lab. The lack of these elements has likely made the "from the lab to the hospital bed and back to the lab"[2] circular model unattainable. Because of its large population, China has the opportunity to build large repositories, or banks, of diseased tissue. However, without implementing an internationally standardized system to manage sample collection, preservation and appropriate utilization, as well as all related clinical information, the value of these precious resources will not be properly realized. To address these issues we believe translational medicine in China should focus on the following aspects: collection, integration, and utilization of clinical resources; development of digital medical decision-making systems and interactive medical information exchange networks in order to solve current problems about uneven distribution of medical resources; emphatically to integrate pharmacological genomics into individualized diagnosis and treatment, to select effective "personalized" treatment regimens in order to improve

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efficacy and reduce medical cost.

Although translational medicine has become a hot topic in China, there still exist two extreme views: one contends that translational medicine not only promotes the progressive development of this country's medicine and health related sciences, but also increases the opportunities for international unification, in addition to providing opportunities for establishing this country's new medical care system, improving the nationwide health level, lowering medical costs, and driving the development of related industries. The other point of view insists that this is purely a gimmick of academic circles. Even if similar disputes are the same in the U. S. , they are currently still freely developing and being debated[3]. For example, in the latest Wikipedia entry for translational medicine, some still believe that the term should be changed to "translational medical science". Furthermore, the numerous American college professors who consistently follow the research model of only caring about creating publications generally clash with an interest in translational medicine instead of welcoming it. This is due to the fact that translational medicine has already surpassed the technological level and has involved policy, regulation, and social development. The difference and debate in understanding is unavoidable. Recognizing translational medicine's implications, scientific connotations, and political significance in this particular moment of scientific history is a special focus of its advent in China that is crucial to the country's health development. This article presents personal thoughts and suggestions on the focuses of translational medicine in China in addition to offering comments.

1 Translational medicine is a product of scientific development that exemplifies political requirements and examines and reforms the current bureaucratization of the medical care system

Translational medicine, originally introduced by the NIH in the United States[1], has become a new field of study and has received government promotion[4]. This in itself reveals the uniqueness of translational medicine's creation. New technology is a main driver of implementing translational medicine, especially developments of big sciences, like human genomic project , in life science that can provide more effective means of directly responding to and solving clinical issues in the human body. The rapid development and "substantial achievements" of basic research have not only not reached the level of clinical diagnosis or surpassed realizing the fundamentals of lowering morbidity and motility rates, but instead have actually increased the medical insurance burden. Additionally, the current foreign procedures and technology evaluation models of the research and application of new medicines limit the survival and development of the most dynamic small and medium sized businesses. This is due to overly lengthy research periods and an overly large degree of long-term deadlock and tacit compliance. The pharmaceutical industry overseas is also gradually becoming a "bureaucratic industry", and has gone one step further by making the embarrassing situation already existing in the health care field worse. This phenomenon must cause people to reflect on the current situation[5,6]. The birth of translational medicine is in itself a product with a close relationship between technology and policy. It emphasizes change in the medical research model and strengthens the close bond between basic and clinical research, as well as accelerating the strategic research and advancement of the industrial development of scientific research achievements. Therefore considering the development of translational medicine from either the technology or policy aspect alone may be too one-sided.

2 Translational medicine in China is an opportunity to revolutionize medical science, but also a one-time opportunity to reform and develop the social medical care system

Although the principle of translational medicine settled recently in China, it has had a huge effect and has become an enormous one-time opportunity for the country's biological medical research, industry, and social services. Firstly, translational medicine has focused on using new principles, stressing our practical research and clinical applications, and promoting the development of the medical industry and social healthcare system. It has a strong government-directed spirit (the inevitable result of life science and social development) . Emphasizing, understanding, and promoting the development of translational medicine will cause the conscious gathering of the foundational study, clinical research, business, and regulation departments under the direction of the government. There will be emerging a new model that will naturally complement the current state of the country's biological medical industry development model and the social healthcare system. Secondly, China's big science technologies in the life sciences, including genomics, proteomics, metabolomics, and high-throughput microarray technologies as well as their related research mechanisms, have already completed technological accumulation, entered the leading stage, provided excellent research platforms to meet the growing demands of clinical research, and promoted these platforms to enter into international

exchange and competition circles. Large amounts of well-trained talents in the excellent foreign institutions have come back China and those repatriate staff members just in time to make up the lack of human resources in foundational and clinical research or bond researches from two sides. So at this juncture China's clinical research and application level can be improved by leaps and bounds, and the "from the hospital bed to the lab and back to the hospital bed" circular model can be formed at a relatively high level.

Translational medicine's 4P (predictive, prevention, personalized and participatory) concept has given the "preventative disease treatment" strategy in China's health activities a strong theoretical foundation and technological support in addition to spurring the development of emerging industries. Information technology (IT) has bettered rational and effective allocation of good medical resources in the health field, which can swiftly reduce healthcare disparities between regions, which is a prominent problem in Chinese healthcare system. The increasing participation of the public will improve the effectiveness of the medical care system. Therefore, translational medicine will effectively promote the rapid development of China's health undertakings in the country's rise and healthy growth.

3 Disparities in the focuses of domestic and foreign translational medicine

Currently the greatest difference between translational medicine in China and the U. S. depends on the disparities in their points of emphasis. China still stresses innovation, the combination of foundational and clinical research in discovering new genes or mechanism, further investigating disease mechanisms and genes related to disease, and determining how to combine lab research with practical application. One goal that is the same for both domestic and foreign translational medicine is getting the starting points of research to guide the way to fulfilling clinical demands. Internationally, it is especially American translational medicine that stresses altering new technology and principles to improve the practical techniques and plans of clinical diagnosis and treatment. Thus, they particularly emphasize intermediate processes, which include strengthening regulatory science researches in close cooperation with the FDA. In this way they can strive to change the rigid preclinical and clinical evaluation processes for the clinical application of recently developed medicines and technologies. This adjusting of current clinical evaluation regulations makes the process more scientific and effective. By applying new technology and screening new medicine targets, new effects can be achieved and the drugs from previous failed clinical evaluations can have another chance to be re-investigate their new clinical utilities in selected populations. These measures and efforts are almost absent in the current domestic translational medicine plan; however, any new clinically applied medicine or technology needs to undergo rigorous evaluations and registration procedures. A lack of any of these crucial elements would make accelerating the modification of new technology, plans, or medicine at the clinical level an impossibility. Thus, translational medicine must merge technology and policy, for a lack of either one would prevent its healthy development. The disparities between translational medicine in the U. S. and China can also be revealed through a comparison of each country's establishments. The leading role of the government is relatively apparent in the construction and development of American translational medicine institutions. The NIH recently established the "National Center for Advancing Translational Sciences" (NCATS), which will take the lead in directing and coordinating every American translational medicine center nationwide by means of the NIH's policies and funding. Since the NCATS has taken these leading actions, it can also have complementary effects on those institutions. On the contrary, translational medicine centers established in China just reflect the requirements of research staff, clinical physicians, and institutions. They lack the top-down design and unified coordination, particularly for institutions that formulate and carry out regulations with the SFDA and similar organizations. These translational medicine centers that already strayed from their focuses at an early stage inherently demand our serious attention.

4 Priorities and focuses for the translational medicine researches in China

In order to guarantee the healthy development of translational medicine in China, clarifying focuses, eliminating misunderstandings, and creating clear goals are currently perhaps the most important steps that need to be taken. Translational medicine was just recently introduced to China, but there are already numerous points of view on the subject, among which there is no lack of fictitious ones being passed off as genuine. Some institutions laid early claim to the title of "translational medicine center", but they have little to substantiate this. They only integrate foundational research and clinical application in the physical connection between the lab and clinical practice. Furthermore, there is a lack of innovation and effectiveness in their operational principles, a lack of resource sharing with related institutions domestic and abroad, and a lack of parallel, accepted international standards. Thus,

more efforts must be taken to increase exchange and discussion for the standardization and internationalization of resources and information. Luckily, the establishment of this publication will provide a great platform from which to realize this goal.

The following sections represents my personal reflections on the issues with the highest priority for the translational medicine in China.

4.1 The collection, conservation, integration, and excavation of clinical resources

The core of translational medicine revolves around enacting effective research on clinical issues, and so clinical patients' information and samples are one core focus. Even in the U. S., there still is not a single institution that would dare claim that all of its clinical databases and sample libraries are standardized or that various other types of medical or biological databases can be used to effectively share data[7]. Domestic conditions in China are even more muddled. The advantage we often mention is our large population, which will benefit medical research with its large number of patients; however, these patients and their treatment process cannot be converted into an effective standardized resource database (including their clinical information and samples). What is even worse is that a majority of the existing databases have serious defects. Some contain clinical information, but lack standard preparation and preservation as well as sustainably usable clinical samples, without which new technology cannot be used properly. On the other hand, some specimen resource databases only have a bunch of clinical samples by a disorganized collection that lack standardization and related clinical information, especially treatment efficacy and clinical patient outcomes, which makes it extremely difficult to perform design and research at a high level. In addition, the owners of these databases regard them as their babies, and so are unwilling to let other people change them and insist on expanding needlessly the databases on their own. Therefore, a top domestic priority is to follow the guidance of the government in gathering the highest level talent with an expertise in establishing clinical data and sample databases. Some other top priorities are to work closely with international institutions in order to formulate an implementable, forward-thinking database that corresponds with international standards and to formulate shared, unified standards. With this foundation an integrated clinical information (dry database) and clinical sample (wet database) database can be established to form a mutually unified clinical information resource database.

A few days ago, BGI-Shenzhen was nationally approved to undertake the building of a "National Gene Bank" in order to provide an opportunity to accomplish this goal. It was proposed that they can compile the academic resources of their domestic and foreign organizations for the purpose of establishing an internationally shared set of clinical "dry and wet database" standards. The established "dry database" will be incorporated into the dry system of the national database and be opened to the public, while the "wet database" will be safeguarded in a previously established institution. These databases will both be incorporated into the national database, where they will be shared by other libraries under standardized protocol. This may be one of the most effective and economical methods of establishing a large-scale Chinese clinical database in line with international standards.

4.2 The development of medical digital decision making systems and the "medical magic mirror"

Another critical clinical application target of translational medicine is to found a medical decision making (MDM) system. MDM emerged on the same day as the invention of computer technology, and although it has experienced a multitude of difficulties, it has still become a focus of investment for commercial establishments such as Google and Microsoft. If a generous amount of patient clinical treatment outcome and prognosis data can be integrated and comparatively analyzed, then the most sensible clinical regime decisions can be made for patients[8]. Furthermore, the information of patients undergoing these clinical regimes can be used to go one step further in editing original systems, expanding database content, and making the decision making system more strategic and powerful. Young doctors using the MDM system can rapidly gain experience previously only attainable through ten years of clinical experience. The speed of young physicians' development will be significantly increased, and every treatment system will undergo a fundamental change. At this stage, can China institute this type of system, and if so, how? I have discussed these questiens with many experts but have received no clear answers. For many questions even the basic information is unclear. For example, how many clinical cases must be collected before a decision making system can be developed for a particular disease? There is still no answer for the question of what crucial information technology issues must be resolved. In a clinical resource database conference session held by BGI-Shenzhen, I called for the establishment of an MDM system that minimizes individualized disparities, which I called a "medical magic mirror". In addition to containing clinical efficacy and outcome data in this system, it is even more important to have genome and metabolism databases that closely reflect drug use target, metabolism, efficacy, and toxicity data. For instance, a pa-

tient suspected of having lung cancer can search the MDM system for information on 10 000 other cases of patients with the same gender, a similar age, and similar clinical signs. Next, that patient could use a "point-by-point comparison" method to find consistencies in EFGR mutations among 3 000 "digital patients". Then he or she could search for metabolism rates of related cytochrome P450 genotypes to narrow the results down to 300 cases, and from this continue a point-by-point comparison of toxic effects and related biomarkers to finally filter out 10 or so his or her "mirror digital patients". At this time we believe that the main individual differences between these examined patients and the "digital patients" filtered out by point-by-point comparison have basically been minimized or even "eliminated", and so the patient has found a case identical to his own in the "medical magic mirror". Thus, the "twin-like" clinical efficacy and outcome results associated with these "digital patients" can give actual patients relatively accurate search results. Establishing this sort of decision making system can greatly reduce the number of cases required to make clinical decisions, which would make it a valuable MDM system. Fortunately, the research team led by Professor Li Jin of Fudan University is already taking a great step forward in improving this system's calculation model. They have established the "JWMDS" MDM system, which is far more effective and efficient than the aforementioned point-by-point comparison model. The system can perform a point-by-point analysis of tens of thousands of clinical cases and can connect information on patients' treatment effectiveness with their prognoses. Characteristic clinical prognosis model cases should be selected as soon as possible in order to test and correct the system.

In addition, in order to gain the sensible distribution and equalization of treatment resources, the use of moble phones and other communication devices to collect patient health data and utilize systems in concert should be a focus of new technology integration. Recently, I visited the newly founded "heart disease center" in the Guangzhou military general hospital, where extremely effective terminal data collection as well as transmissions and central command coordination centers have been established. The time elapsed from discovering a myocardial infarction to the beginning of heart surgery can be cut down to 30 minutes (the international standard is 90 minutes). There are two key factors that allow this achievement to occur: core digital technology is one factor, and the clinical office coordination and operational model is another factor even more important to success in China. This further illustrates the characteristic merging of technology and strategy that define translational medicine.

4.3 Pharmacogenomics and personalized medicine

In accordance with the aforementioned system, domestic research application areas that have developed relatively rapidly in recent years include pharmacogenomics and personalized medicine. Pharmacogenomics is the most direct bridge between genomics and personalized treatment. The biomarkers provided by the pharmacogenomics research institutions can directly guide rational medication. Not only do they greatly increase medication efficacy and reduce toxic side effects, but they also can prevent the accidental overdose of medication given to patients and reduce medical costs[9,10]. In regards to the clinical application of small molecule and antibody drugs for targeted treatment of lung cancer, breast cancer, colorectal cancer, and lymphoma, some large hospitals have already begun to use "companion diagnosis tests" based on molecular typing, which guides doctors in medicating "precisely" and producing great results. Some medium and small size companies dealing with the research and development of these sorts of testing kits are growing relatively quickly in China. For instance, within a few years after the development of "companion diagnostic kits" for targeted anti-cancer drugs by Amoy Diagnostics in Xiamen, it had gained SFDA registration and CE certification. This technology has reached an international level, and was appointed by the multinational pharmaceutical company Astrazeneca to be the clinically used concomitant diagnostic kit for Iressa and other anti-lung cancer targeted drugs.

The research team led by Central South University's Academician Honghao Zhou is a pioneer in Chinese pharmacogenomics, and in recent years they have gotten striking results while promoting personalized medicine. It is worth mentioning that they have already established a digital decision making system that can effectively guide drug treatment for various diseases. By first measuring the genome and activity of isoenzymes related to drug metabolism (P450) in patients, it is possible to effectively provide "accurate" medication of related drugs for people in the future, and so realize a new medical model I called the "plan treatment before patient hospitalization".

Due to China's benevolent development in this field and the fact that it already had a very good foundation in crucial research and industrial technology, the research focus for the combination of translational medicine and basic clinical research should be organizing and analyzing standards for the collection of data and samples related to the treatment effects of each clinical line of medication in addition to those of new drugs. The results of this type of research not only reinforce our understanding of patho-

genesis and produce high level research papers, but also will soon become an industry that can test related biomarkers to realize personalized clinical treatment with higher efficacy, lowered toxic side effects, reduced medication, and lowered hospitalization rate costs.

This point is also very important to society. We hear grumbling complaints in China all of the time that "we can't get the best medicine", and they believe that the best medicine is always the newest and most expensive medication. The implementation of the theory and practice of pharmacogenomics and personalized medicine will ultimately make the public understand that the "best medicine" that they need is that which is the most effective and has the least toxic side effects on the basis of each individual patient, and at times this may actually be the cheapest medicine. This change in principle is significant in solving our current overall lack of medicine and medication as well as the social phenomena of ubiquitous overmedication and wasting of drugs. Reducing overall medical costs may be a new revolution for society.

4.4 Translational science and related regulatory sciences

As was previously mentioned, translational medicine is both a technological aspect and a strategic innovation. This point is embodied especially clearly in the tasks and goals of the newly established "National Center for Advancing Translational Sciences" according to the currently appointed NIH Director Collins, who also set up the NIH funded NIH-FDA regulatory science research program. The goal of this project is to formulate and provide a solid scientific foundation for regulations on the research and development of new medication and treatment technologies as well as the evaluation and clinical application of new modes of implementation. For example, his regulations clearly promote the launch of phase zero clinical testing (this was previously known as the "micro-dosing clinical trial") and the establishment of drug tracing technology. If the system can be perfected in terms of drug development, not only could it expedite the process of evaluating a drug's clinical effectiveness, but also it may be possible to "jump" the preclinical research process, which would greatly shorten the drug development time and reduce development costs. Domestically this field is almost empty, and some severely disruptive differences between China and other nations include a relatively small amount of new diagnosis and treatment technology, such as the clinical evaluation and application of cell and gene therapy technology. Additionally, the examination and approval process is currently almost at a standstill, and some even dispute the right of attribution in this process! Apart from the rigidity present in the administrative management of examination and approval mechanisms and the outdated concepts that need to be changed, another important reason for this is a lack of sufficient regulatory science investment and research. Also, technological and scientific problems related to safety and treatment efficacy lack a solid digital foundation, which reduces faith in examination and approval mechanisms. These problems also exist to a different extent in the U. S. , and they have become a focus of Director Collins. As a result, he is establishing an order of business shared between research and development mechanisms, clinical institutions, and examination and approval mechanisms (SFDA). This is best done through official coordination and direct cooperation between the NIH and the FDA and through adding to their already established allied regulatory science research on biological treatment. As a means of providing international standards, shared examination and approval guidelines can be jointly prepared. These steps would drive not only China's but also international biological treatment development.

5 Suggestions

5.1 Strengthen organization and formulate Chinese standards that comply with shared international clinical information and sample library standards

By borrowing the resources of the "National Gene Bank", organize domestic and foreign experts, and learn from the already matured and recognized clinical information and sample preparation guidelines set up by the SOP that suit the state of the nation. In this way the standardization and internationalization of domestic clinical information and sample preparation and protection can be achieved. An expert committee responsible for sample library construction, instruction, and validation should be built on this foundation. The validated sample library should be incorporated into the national library as a sub-library and be opened to the public. The national government should provide continual and appropriate financial aid.

5.2 Strengthen clinical drug genomic research and promote personalized medicine

Organize a large clinical sample resource database of drug responses that focuses on investigating the underlying mechanisms of the toxic side effects of basic and new drugs and promotes the research and development of new drugs. Meanwhile, enhance the industrial development and clinical application of biomarker-based personalized medicine.

5.3 Strengthen and accelerate the construction of MDM systems and make standard strategies the top priority

Make full use of China's internet and communication

advantages to accelerate the formation of digital medicine and bring about the equal distribution of medical resources. Particular attention should be paid to issues of unifying standards and sharing at the initial stage. Taking major established national scientific and support plans as leading examples and established systems (such as the Zhejiang provincial digital medicine system) as models, improve efficiency and avoid waste.

5.4 Intensify medically related regulatory science researches

Establish approval and market access mechanisms that are able to promote China's new medical development, and integrate as much as possible into international plans. Ensure that China's biomedical regulations and guidelines are synchronized with and on the same level as international ones, and accelerate the clinical application of new diagnostic techniques. In major national specialized projects for new drug development, establish a committee composed of international talent with experience in working for the FDA and/or similar American regulatory agencies and in the research and development of new drugs as well as SFDA researchers. Have this committee cooperates with the NIH and FDA to jointly investigate the development of related regulatory sciences and promote translational medicine's development and internationalization.

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