转化医学研究（电子版）2011，1（2）：44－55
Translational Medicine Research（Electronic Edition），2011，1（2）：44－55

Review



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Editorial note：*Biobanks are unified resources that include bio specimens，phenotype data，molecular information generated from the specimens. It plays an irreplaceable role in the studies of human disease prediction，diagnosis and treatment. Recently National Supporting Plan supported creative study in this field. This review emphasized the development and problem existed and put forward to hope in bio sample types，contents，sample scales，sample standardization，quality control，ethic protection and resource sharing requirements. We believe that readers will better known the importance of biobank and translational medicine research.*

Biobank and translational medicine

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Abstract　Biobanks are unified resources that include bio specimens，phenotype data，molecular information generated from the specimens. It plays an irreplaceable role in the studies of human disease prediction，diagnosis and treatment. The emergence and development of the translational medicine has posed an increasing requirement to the bio samples resources. Biobanks are evolving from single centered to multi centered and national scale. As the foundation to the translational medicine，biobanks need to be improved，so to fulfill the bio sample types，contents，sample scales，sample standardization，quality control，ethic protection and resource sharing requirements posed by the translational medicine.

Key words　biobank，translational medicine，translational research

Biobanks are nothing new. Its first emergence can be traced back hundreds of years ago. From the application of diagnosis to treatment，then to life science，the continuously developing human society has granted biobanks more and more meanings.

The availability of the complete sequence of the human genome，annotated with a comprehensive catalogue of genes and sites of sequence variation（polymorphisms），has opened up new possibilities for research into genetic effects on human health as well as possibilities for the development of new diagnostics and treatment modalities[1]. Discovering biomarkers，and use them effectively in the process of disease prevention，diagnosis，treatment and the development of

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novel medicine, it has become more and more important in the post-genome era which aims to provide personalized treatment to the patients. The rapid development of molecular biotechnology and bioinformatics has formed a solid ground for life and medicine research. The life science is reaching a deepness and wideness that has never been reached, and more scientific discoveries are increasingly emerged. Unfortunately, clinical validation of these costly discoveries has proceeded at a slow pace [2]. Most basic research discoveries stayed far from clinical practice. To correct this imbalance between discovery and validation, translational medicine is advocated and has rapidly progressed to be the hot-spot in in the field of biomedical research. The key to translational medicine is to integrate seamlessly bench and bedside[3] . That is, to rapidly translate the newest discoveries in laboratory to the novel clinical technology or products (bench to bedside), as well as to translate the real world issues to the labs to guide new or further studies (bedside to bench) . So, a proactive research loop is formed based on the clinical requirements.

Biobanks are important carriers to integrate basic research and clinical application. By integrating clinical data together with genetic data, a biomedical information resource platform that is organized by individual is then formed. It will play an important role in providing fundamental and strategic resources to translational medicine. With modern biomedicine evolving to molecular medicine and personalized healthcare, biobanks are facing new opportunities as well as challenges.

1 Definition

Biobank, as defined by the OECD, is a structured resource that supports the research of genome. It includes bio samples from the human body (blood, urine, tissue, DNA, cells, etc.), the information generated from the study of the bio samples, as well as the enormous data related (demographic, diagnosis related, life style, environmental exposure, etc.)[4]. Different goals and designs of studies will affect the form and content of the biobanks. But the biobanks can be categorized as the following two basic types[5]: (1) population-based biobanks, which accommodate the specimens and related data including genealogy, lifestyle, environmental exposures etc., from randomly selected volunteers. These resources can be used not only in the study of the natural frequency of occurrence and progression of common diseases, but also in exploring the biomarkers to identify the onset of diseases or susceptibility. (2) disease-oriented biobanks, which may contain specimens and related clinical data from patient or case control healthy individuals. These materials can be used to find the biomarkers for diagnosis of a disease or prediction of disease progression and novel therapeutic target as well.

Translational medicine is also known as translational research, a new sub-discipline proposed in recent years in life science. It means "from the laboratory to the bed (bench to bedside)" and "from the bed to the laboratory (bedside to bench)" bidirectional translational research, referred to as B2B[6]. The essence of translational medicine is the integration of theory and practice, laboratory and Clinic, multi-disciplinary, multi-leveled, micro and macro, static and dynamic, structural and functional, physiological and pathological, preventional and treatment targeted, humanitical and scientifical.

Undoubtedly, biobanks have now become the cornerstone of translational medicine. They promise to provide high quality bio specimens and technical services for discovery and validation of biomarkers related to disease prediction, prevention, diagnosis and treatment.

2 Biobank activities over the world

Rapid progress in molecular biology and translational medicine, leads to rapid increasing requirements for large-scale, high-quality biological specimens and related information resources. Therefore, the biobank application is emphasized by many developed countries, research institutes, and pharmaceutical companies as the strategy to improve their core competiveness in the biomedical field.

Since 1990s, various biobanks have been constructed around the world. At least 179 biobanks with 345 000 donors exist in the U. S., most of which were established in the last 10 years [6]. At the same time, Biobanks also proceeded in fast pace in some developed country from Europe to Asia. In 2010, JRC-IPTS (Joint Research Centre, Institute for Prospective Technological Studies) issued a report about current biobanks activities in Europe. Although the report is from Europe, to some extent it can reflect the overall situation around the world. Among the investigated 126 biobanks from 23 countries, few of them identified started collecting bio samples in the 70's, they have been built up relatively recently (about 40% during the 90s) with 37% of the surveyed biobanks starting their activity after 2000[7]. The survey completely illustrates the rapid trend of biobanking. Some other indicators from the investigation are also interesting. Such as 70% operated in single-center mode; 80% managed by universities or government agents; 85% experienced multilateral cooperation; 52% involved international cooperation. Most biobanks are small or medium scale, where the number of disease specific biobanks is comparatively

more [8].

Although the extensive development of biobanks have met in some aspects the specimen requirements of certain researches, something important is neglected. That is the lack of unified standardization systems for underpinning the development of biobanks, which involves terminologies, identifications, data structures, SOPs, quality criteria, sharing mechenisms, ethics protections, privacy and safety guidelines etc. Just because of that, exchanging and sharing bio specimen and attached information between different biobanks become a more challenging mission to the society. But In real world, many large-scale researches often need massive specimens, which is far beyond one or even several biobanks' capacity. Therefore, the silo problem must be solved to guarantee the sustainable development of biobanks. Some countries began to establish a national biobank (Tab. 1) to promise the resource supply, which represents an important trend of current international biobanking.

In addition, some international organizations, including ISBER (International Society for Biological and Environmental Repositories), P3G (Public Population Project in Genomics), BBMRI (Biobanking and Biomolecular Resources Research Infrastructure), IARC (International Agency for Research on Cancer), CaBIG (Cancer Biomedical Informatics Grid), OBBR (Office of Biorepositories and Biospecimen Research) etc., are all devoted to promote the harmonization of biobanks development. Their works are focused on various aspects of standardized biobanking, involving best practice, technical standards, quality control, resource sharing, ethics, etc., which contribute to a solid foundation for sustainable biobanking. The foreseeable future of the biobank should be more specimens with the feature of large-scale, standardization, networking and digitalization.

3 Biobank for translational medicine

Massive studies have discovered that to translate into clinically available technologies and products, researches need to go through at least two phases of validation works. Firstly, the results of the research need to be validated to be TRUE, but not artificial illusions caused by non-proper analytical methods. Secondly, a prospective study need to be done to further confirm the results of the basic research, either a new diagnosis or a new treatment method, can improve the results for the patients. In these two phases of validation, biobanks are always playing an important role, as it becomes the non-missable technical supporting tool to the entire translational process. Hence, the biobanks are the fundamental platform to the whole translational medicine system (Fig. 1).

The rapid development of translational medicine has pushed the construction and development of biobanks to higher standards. It involves the type, content, scale, standards system, quality control, informed consent, sharing mechanism, etc.

3.1 Type

Translational medicine not only requires disease specific biobanks, it also requires population specific biobanks. These two types of biobanks have relatively complemented the translational medicine. Based on disease based biobanks, researchers can realize studies on how the genome and disease are correlated, therefore to identify disease related genome formula. On the other hand, population specific biobanks can validate the discoveries found during the studies of full spectrum of genome relations. To combine the studies based on these two types of biobanks, the validation process will be accelerated.

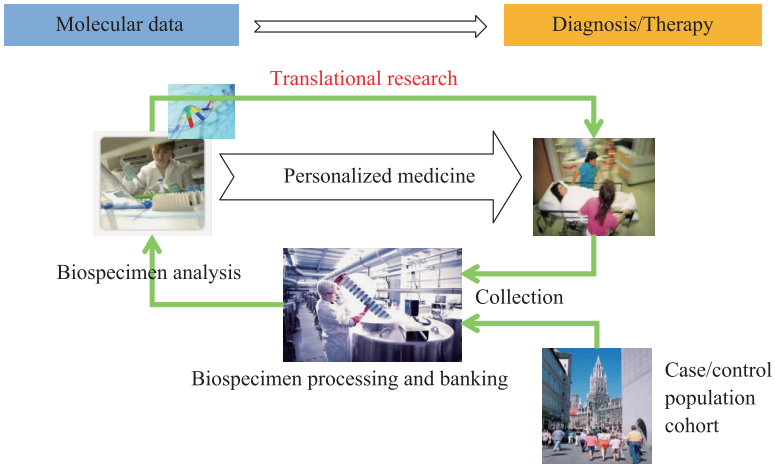

Fig. 1 Biobank in translational medicine system[9]

Tab. 1 International Biobank Projects

Project	Type	Start time	Content	Goals
Icelandic Biobank Iceland	Population-based	1996	Genotypic and medical data from more than 140 000 volunteer participants.	To lead the world in the discovery of genetic risk factors for common diseases and in turning these discoveries into diagnostic tests for assessing individual risk of disease.
Estonian Gene Bank Estonia	Population-based	2002	Phenotype (Health data, geneaology data, lifestyle, environmental factors and drug response) and tissue samples from 1 million vol-	To establish national Gene Bank, carry out scientific research, genetic and health studies, find the genes that cause disease and influence common disease.
UK biobank British	Population-based	2003	Collect genetic samples from half a million volunteers aged 40 ~ 69, combined with their medical information.	To study how the health of 500 000 people, currentl yaged 40 ~ 69, from all around the UK is affected by their lifestyle, environment and genes. The purpose of this major project is to improve the prevention, diagnosis and treatment of a wide range of illnesses (such as cancer, heart disease, diabetes, dementia, and joint problems) and to promote health throughout society.
Biobank Japan Japan	Diseased-oriented	2003	Create a large-scale DNA repository, with blood samples from some 300 000 individuals.	The project aims for construction of basic information for personalized medicine
Hunt Biobank Norway	Population-based	2007	Whole blood and DNA from 200 000 individuals; serum and plasma samples from more than 100 000 individuals as well as urine, RNA tubes, cells, buffy coat; Na-heparin tubes from 50 000 individuals. HUNT studies have compiled extensive medical, lifestyle and environmental data associated with each biological sample, comprising in total about 800 exposure variables and nearly 3 000 different variables per individual.	HUNT collaborates with national and international research groups on some of the most important health challenges facing our world today, such as diabetes, cancer, musculoskeletal disease, mental illness, migraine, prostate problems, urinary incontinence, reproduction, weight and cardiovascular disease. HUNT data can be used within biomarker validation, studies on disease specific cohorts and post marketing investigations for health economic and safety assessments.
caHUB	Diseased-oriented	2009		2009caHUB aims to modernize the field of biobanking by developing an infrastructure for collaborative biospecimen research and the production of evidence-based biospecimen standard operating procedures. caHUB will make the resulting data, analysis, policy documents, and scientific tools publicly available to enable the community to collect biospecimens fit for specific scientific purposes.
Lifegene Sweden	Population-based	2009	Blood and urine will be collected from 500 000 volunteers, as well as the questionnaire and health check.	To further understand how gene, environment and life style affect human health

3.2 Content

Unlike traditional biobanking, the biobanks for translational medicine collects richer content, including sample entity, phenotype data and genotype data. The granularity of phenotype and genotype information directly determines the value of the biobanks. In general, phenotype information should contain donor's all medical information, demographic, family, lifestyle, occupation, and environmental exposure etc. Different study designs often leads to flexible granularity. Take family history for example, the detailed information may expand from only parent to cover brothers, sisters and children. Genotype information means molecular level data all generated from laboratory analysis and tests. These micro-level data should also be part of the biobanks. Efficiently sharing above data can help avoid wasting valuable specimens to "reinvent the wheel".

3.3 Scale

The rise of translational medicine can be a serious challenge to the scale of biobanks. Both basic research and its validation requires tremendous amount of bio-samples. Lesser samples can affect the analytical results, causing deviations of the authenticity and accountability of the discovery and its validation. Traditional small to medium scale biobanks can hardly fulfill the resource requirements raised by the translational medicine. The lack of samples resources has already limited the development of translational studies. To realize the enlargement of biobanks, there are two solutions at hands. One is to build a super scale national biobank. The scale can be hundreds of thousands or even millions in population. Examples are UK BIOBANK, the LigeGene of Sweden, the Estonia Gene Bank, etc. The other one is to consolidate the now existing biobank resources, to form an integrated, shared resource network, such as OnCare UK, caBig of the U. S., CHRNet of Canada, P^3G of Europe, etc. A super scale biobank can take years to build, while integrating current biobanks always face standardizations problems. So pairing these two methods can be the trick.

3.4 Standards

Translational studies require consistency of the bio samples resource, so to ensure samples and the information gathered from the samples from different donors, different facilities and on different time are comparable, is a very important precondition to the validation works of translational studies. As some major translational studies arise, the scattered individual biobanks will ultimately go to consolidation. The consolidation works can be hardly done without standards. Currently, international standards system is still in absence. Although some of the international standards organizations are working on it (WHO, IARC, RAND, OECD, NCI, etc.), and have issued some reputable guidelines, the guidelines are not able to fully inhibit every biobank. The constructions of biobanks are more or less localized. This present situation poses a potential risk on the sharing of the resources of the biobanks.

Setting up a standards system on the construction of the biobanks is critical. It involves all the aspects of collection, process, storage and application of the bio samples.

3.4.1 Standardized workflow

Following a standardized workflow makes it possible to clearly define every process of the biobanking activities. So, a comprehensive framework of the standards system of biobanks can be initiated with regards to the process tasks, executors, control and interfaces.

3.4.2 Standardized operation

In each phase of the construction of a biobank, refined SOPs should be setup to guide the flow and processing of bio specimen. For example, a unified informed consent template is required in phase of consent; qualification of donor should be clearly defined in phase of enrolment; the specific time, position, operation and instrument etc. should be emphasized in phase of collecting; the data range, source and means of collection should be predetermined in phase of information acquiring; and operational qualification, measures, device, and consumable material are also very important aspect in phase of processing. Following these standards jointly is the only way to ensure the consistency of bio specimen and associated data.

3.4.3 Standardized data

Standardized data means the requirements to unify the data definition, expression, value range etc., which guarantee the data consistency. In this aspect, some mature international medical standards such as SNOMED, ICD9/10, LIONC, DICOM, should be referenced at first.

3.5 Quality control

Setting up a comprehensive quality control system is a unavoidable fundamental work. It has been neglected for quite a long time[10]. The SOPs used by the biobanks are lack of the support of evidence. The collection and storage process of bio specimen are affected by different 'skills' and 'experience', thus, can be hardly evaluated objectively.

Studies on the quality control of the bio specimen are urgent for setting up high quality biobanks. Just as what NCI OBBR and SPIDIA are doing, identify the risk factors, improve the quality tracking system, build up the SOPs based on evidence and quantifiable quality eval-

uation systems (histological analysis, quality-indicator biomarkers, etc.) are the keys to preserve quality bio specimen.

3.6 Informed consent

Differed from traditional medical studies, biobanks are more future oriented, the way to use and dispose of the bio specimen are uncertain[11]. So while the traditional Informed Consents are not suitable, an over generous Informed Consent could bring unpredictable ethic problems. A hierachical Informed Consent or a generous Informed Consent monitored by a third-party are the two choices we have for bio specimen collection.

3.7 Sharing mechanism

Close collaboration between the clinical and Laboratory sides is important during the collection of bio specimen and its data resources. Large scale translational studies are depend on the collaboration among biobanks. So to build a bio specimen and its related data sharing mechanism is necessary. It should follow the 'hierachical sharing, pay for use' rule. Through quantitative evaluation of the bio specimen and its related data, and profit sharing system, donors, clinical and laboratory sides are all granted reasonable returns. It will ensure the continuous development of the biobanks, thus provide a steady flow of high quality resources to the translational studies.

4 Conclusion

China is on its way to an innovation-oriented country. Life science and bio-medical studies are also facing new opportunities. Although China has a latter start in translational medicine, but the development has been rapid. As for now, more than 30 multiple levels of translational medicine platforms are being formed. As the cornerstone to the whole translational medicine system, the construction and development of biobanks should be valued by the government and industry. By drawing lessons from the predecessors, create suitable guidelines, quality control systems and sharing mechanisms, will promote the Chinese biobanks to a higher level, and translate the wealthy clinical resources in China to an invaluable treasure to support the studies and development of life science.

Acknowledgement: We thank the team of Beijing Biobank Project for their great support.

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