China Biobanking Strategy for Integrated Translational Research

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Shanghai Clinical Research Center
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Outline of Biobank Development in China

The strategy for China Biobanking

Translational Researches based on Biobank Initiatives
Background

- Vast resources: clinical specimen on a large scale with clinical information
- One of the basic platforms for Translational Medical Research & New Drug Development
- Promote the investigation in disease mechanisms & biomarker identification
1994 The Chinese Academy of Medical Sciences started to work on establishing a bank of immortalized cell lines of Chinese ethnic groups.

1998 The Ministry of Science and Technology of China (MoST) and the Ministry of Health of China (MoH) drafted Human Genetic Resources Managements for Trial Implementation.

1998 The Office of Chinese Human Genetic Resources Management was set under the Ministry of Science and Technology of China.

2001-2005

2002-2007 NICGR was published online.


2007-2010

2008, Shanghai Municipal Science and Technology Commission launched the project of Shanghai Clinical Biobank Research Center.

2010 Clinical Specimen Repository was initiated in the context of Significant New Drugs Development with the support of the MoH and MoST.

2009 Beijing Municipal Science and Technology Commission launched the construction of Beijing clinical data and sample repository of major diseases.

2011-2015

2012 Human Genetic Resources Management Regulations (draft) was formulated by the Office of Chinese Human Genetic Resources Management.

2012 Shanghai Biobank Engineering Research Center has officially granted as Shanghai Municipal Biobank Center by Shanghai municipal government, and the construction of Shanghai Clinical Biobank for Major Diseases was launched.

2003 The National Infrastructure of Chinese Genetic Resources(NICGR) was initiated as an important part of the National Science and Technology Infrastructure Program by the Ministry of Science and Technology of China.


2007.9 NICGR was published online.

2009 Beijing Municipal Science and Technology Commission launched the construction of Beijing clinical data and sample repository of major diseases.

2010 Shanghai Municipal Science and Technology Commission launched a project for the setup preparation of Shanghai Biobank Engineering Research Center.
<table>
<thead>
<tr>
<th>Year</th>
<th>Project</th>
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</thead>
<tbody>
<tr>
<td>1994</td>
<td>Immortalize Cell Bank of Different Chinese Ethnic Groups</td>
</tr>
<tr>
<td>1998</td>
<td>Human Genetic Resources Managements for Trial Implementation</td>
</tr>
<tr>
<td>2003</td>
<td>National Infrastructure of Chinese Genetic Resources</td>
</tr>
<tr>
<td>2009</td>
<td>Beijing clinical data and sample repository of major diseases.</td>
</tr>
<tr>
<td>2010</td>
<td>Clinical Specimen Repository in the context of Significant New Drugs Development</td>
</tr>
<tr>
<td></td>
<td>Shanghai Biobank Engineering Research Center.</td>
</tr>
<tr>
<td>2012</td>
<td>Human Genetic Resources Management Regulations (draft)</td>
</tr>
<tr>
<td></td>
<td>Shanghai Clinical Biobank for Major Diseases.</td>
</tr>
<tr>
<td></td>
<td>Shanghai Biobank Engineering Research Center</td>
</tr>
</tbody>
</table>

- Platform-based integration of government and local resources
- Establishment of Chinese clinical biobank and database
- System innovation, sustainable model of development
- Specimen resources sharing mechanism

- Malignant tumor
- Cardio-cerebro-vascular diseases
- Neuropsychiatric diseases
- Metabolic diseases

- New drug discovery
- Major disease mechanism research
- Standardization
- Reflect the epidemic characteristics
The National Biobank Network in China

**Beijing:**
- Peking Union Medical College Hospital
- Xuanwu Hospital, CMSU
- Cancer Institute, Tianjin University
- Cancer Institute, Beijing University
- Fuwai Hosp. of Cardiovascular Diseases, CAMS
- 1st Hospital, Beijing University
- General Hospital of PLA (301 Hosp.)
- Beijing Anzhen Hospital, CMSU
- .......

**Shanghai:**
- Shanghai Clinical Research Center
- Shanghai Cancer Center
- Zhongshan Hospital
- Huashan Hospital
- Obstetrics and Gynecology Hospital
- Reijin Hospital
- Renji Hospital
- Shanghai 6th people’s Hospital
- Shanghai 9th people’s Hospital
- Xinhua Hospital
- Shanghai Chest Hospital
- Shanghai Children’s Medical Center
- Shanghai Mental Health Center
- Chang Zheng Hospital
- Shanghai Pulmonary Hospital
- .......

**Other regions:**
- Guangzhou: China national gene bank
- Taizhou: large-scale cohort study
- Yunnan: Immortalized Cell Line Bank
- .......

www.scrcnet.org
1. Potential Customers

- The 2nd Military Medicine University (3 Hospitals)
- Shanghai University of Traditional Chinese Medicine (5 Hospitals)
- Tongji University (6 Hospitals)
- Shanghai University of Traditional Chinese Medicine (5 Hospitals)
- The 2nd Military Medicine University (3 Hospitals)

Major diseases (2011-2015)

- Malignant tumor
- Metabolic diseases
- Neuro-psychiatric diseases
- Cardio-cerebro-vascular diseases
- Other diseases & Cohort Study

Clinical Research

Translational Research

Coordination

Support

Standardization

QA & QC

Central Storage

Training

Central IEC

Data & Info

Technical service

Public Service Platform (SCRC)
Outline of Biobank Development in China

The strategy for China Biobanking

Translational Researches based on Biobank Initiatives
Basic Principles for China National Biobank

Non-profit/independent Services

Medical Institutions
- Technical Support
  - Technical standards
  - Standardized sample and data collection
  - QA/QC
  - Research outcomes

Government
- Performance Assurance
  - Central Government: Plan, Project, Policy
  - Local Government: Place, Fund, Personnel
  - Supervise

Social Resources
- Operating Assurance
  - Resource Integration
  - Full-time Staff
  - Maintenance
  - Service
Platform for National Biobanks

Comprehensive diseases

Major diseases

Chinese gene bank

Biological information

Normal specimen

Other Biobank

Standard specimen

Virus

Bacteria

Cell line

Mycoplasma

Animal

Plant

Human

Epidemiology

Minority population

Regional population

National Biobank Projects supported by MOST and MOH

One of 16 National Key Projects: New Drug Discovery and Development
The National Disease-based Biobanks in China

- Step 1: National Biobank in Beijing and Shanghai
- Step 2: Spread to other regions when matured
The Working Flow for China National Biobanking

For Safety / Efficiency / Traceability

Disease maps for health management
Reference for translational research
Key resources for medicine industry
National Key Projects: New Drug Discovery & Development

New Drug Discovery & Development for 4 Major Diseases

Peking Union Medical College Hospital

Coalition Hospitals

6th People’s Hospital, Shanghai
Xuanwu Hospital, CMSU
Cancer Institute, Tianjin University
Cancer Institute, Beijing University
Fuwai Hosp. of Cardiovascular Diseases,
1st Hospital, Beijing University
General Hospital of PLA (301 Hosp.)
Beijing Anzhen Hospital, CMSU

Beijing Biobank for Major Diseases

Phase I target (2009-2012)
- Clinical cases 45,930, total samples 422,489
- Promoted 863, NSF, BSF projects

Phase II target (2013-2015)
- 14 biobanks
- 100,000 cases & 1,000,000 samples

- Collection of high quality specimens
- Complete clinical information
- Informatics platform
Shanghai Disease-based Biobanking Project

Coordinator: Shanghai Shenkang Hospital Development Center

Third Party Service: Shanghai Clinical Research Center

Centralized biobank

- Informatics platform
- Third party service (SCRC)

Standardized system

- Entrust Storage
- Public Storage
- Backup Storage

Quality control system

24 hospitals satellite banks

Public Storage

Backup Storage
Bio-sample Storage

Three Models:

- **Public Storage**
  - Common Disease
  - Sample Sharing

- **Backup Storage**
  - Orphan Disease
  - Special Samples
  - Remote backup

- **Entrust Storage**
  - Community Hospital
  - Institution and Pharma.
  - Storage and Management
Quality Management

<table>
<thead>
<tr>
<th>Works</th>
<th>Stage I</th>
<th>Stage II</th>
</tr>
</thead>
<tbody>
<tr>
<td>QM System</td>
<td>1. Normative work flow</td>
<td>1. ISO 9001 accreditation</td>
</tr>
<tr>
<td></td>
<td>2. Detailed SOP and forms</td>
<td>2. ISO 27001 accreditation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. CAP accreditation</td>
</tr>
<tr>
<td>Quality Control</td>
<td>1. ISBER PT program</td>
<td>1. QC items checklist</td>
</tr>
<tr>
<td></td>
<td>2. DNA Qualification</td>
<td>2. Method Validation &amp; PT</td>
</tr>
<tr>
<td></td>
<td>3. RNA Integrity</td>
<td>3. Quantitative VS Qualitative</td>
</tr>
<tr>
<td></td>
<td>5. Temperature Monitor &amp; Alarms</td>
<td>5. Tissue Antigenicity &amp; Histology</td>
</tr>
<tr>
<td>Inspection</td>
<td>1. Professional team</td>
<td>1. Documents / onsite Inspection</td>
</tr>
</tbody>
</table>

- **BEC-QH-01** Quality Target and Quality Policy for Biobank
- **BEC-PF-01** Confidentiality Control Procedure
- **BEC-PF-10** Preventive Measures Management Procedure
- **BEC-PF-23** Sample Management Procedure
- **BEC-SOP-GA-4007** Liquid Nitrogen Container SOP
- **BEC-SOP-ML-1004** White Blood Cells Collection SOP
- **BEC-SOP-ML-1009** Sample Transfer SOP
- **BEC-SOP-ML-1005-01** Sample Reception Form
- **BEC-SOP-ML-1008-01** Sample Delivery Form
Technology Support

Over 800 Clinical & Bio-lab Tests

Clinical Laboratory Testing Division

- Clinical Immunology Lab
- Clinical Biochemistry Lab
- Clinical Microbiology Lab
- Clinical Molecular Biology Lab
- Hematology/Urianalysis Lab
- Flow Cytometry Lab
- Elemental Analysis Lab
- Cytogenetics Lab

Analytical Chemistry Division

- Pharmacokinetics/dynamics lab
- Chemistry/Drug analysis
- LC-MS technologies

Clinical Pathology Division

- Anatomic pathology
- Cytopathology
- Molecular pathology

Molecular Analysis Division

- Real-time PCR
- SNP analysis
- Gene sequencing
Quality Control

Shanghai Disease-based Biobanking Project
(SCRC + up to 24 clinical biobanks)

Working flow

QC protocol
Ethical Guidance

Ethics Committee is chaired by Dr. Ching-Li Hu

- Member of the UNESCO International Bioethic Committee;
- Senior Adviser and Emeritus Professor, Ruijin Hospital Shanghai Jiaotong University School of Medicine;
- Director of the Advisory Group, Department of Ethics, Legal and Social Issues, Chinese National Human Genome Center at Shanghai;
- Member of the Ethics Committee, Ministry of Health;
- Former Assistant Director-General & Deputy Director-General of the World Health Organization.

- “The Ethics Committee of Shanghai Engineering Research Center of Biobank” established in May, 2012
- “The Ethics Guideline for Biobank” is issued in July, 2013
Data Storage and Management

Cloud informatics: > 39 millions cases so far

Software Copyrights:
- Clinical Specimen Resource Management and Assistance System V1.0
- Clinical Specimen SOP Management System V1.0
- Clinical Specimen Resource Ethics Audit Management System V1.0

Software Features:
- SAAS mode
- In reference to Oracle B/S;
- In conform to NIH caBIG standards
- Project oriented
Shanghai Clinical Information Platform

Up to 2014.3:
- 38 hospitals in Shanghai
- 6000 clinic outpatient offices
- 5100 inpatient offices
- 2900 clinical Labs
- 39 millions cases

Clinical Data

Appointment system
Patient info. platform
Imagining info. platform

Medical Coordination
Patient database

Management & Supervision
Diagnostic database

Safety alarm for therapeutics
Platform data statistics

Clinical data management / Support system
System Validation & Information Security

System Validation:
- The computer system validation strategy
- 21 CFR Part 11 plan
- Validation of the plan and the confirmation
- Risk assessment
- Software development
- Validation of the Database Room
- Quality Validation Plan
- Installation Validation
- Performance Validation
- Operation Validation
- Installation of hardware and software
- Validation of the standard computer configuration
- Business continuity plan
- Disaster recovery plan
- … …

ISO27001:
- Information Security management manual
- Corrective Action and Preventive Action
- Computer management
- Backup management
- Database management
- Visit control management
- Information security management system
- Business continuity management system
- Change management
- Server management
- … …
1. Outline of Biobank Development in China

2. The strategy for China Biobanking

3. Translational Researches based on Biobank Initiatives
The Science of Biobanking

A Proposed Approach to Informed Consent for Biobanks in China
Min Liu¹ and Qingli Hu²
Article first published online: 5 JUL 2012
DOI: 10.1111/j.1467-8519.2012.01985.x
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Bioethics

Shanghai DNA QC Program
- Precision
- Accuracy
- Linearity
- Westgard’s Rules
  - Performed every month
- Proficiency Testing (PT)
  - Program organized by ISBER

Ruan. et al. Biopreservation and Biobanking, 2014 (under revision)
The Research Relevant to Biobank

GWAS in China: Psoriasis, Vitiligo, SLE & Leprosy

GWAS for Psoriasis: Susceptibility variants within LCE gene cluster at 1q21

Psoriasis genome-wide association study identifies susceptibility variants within LCE gene cluster at 1q21

Xue-Jun Zhang1,2, Wei Huang3,4, Sen Yang5,6, Liang-Dan Sun1,2, Peng-Yu Zhang3,4, Qi-Xing Zhu1,3, Fu-Ren Zhang1,4, Chi Zhang1,4, Wen-Hui Du1,2, Xiong-Ming Pu1,2, Hui Li1,2, Feng Li Xiao1,2, Zai-Xing Wang1,4, Yong Cai1,4, Fei Hao1,4, Jie Zheng2, Xue-Qin Yang1,4, Hui Cheng1,4, Chun-Di He1,4, Xiao-Ming Liu1,2, Li-Min Xu1,2, Hou-Feng Zheng1,2, Shu-Mei Zhang1,2, Jian-Zhong Zhang1,2, Hong-Yan Wang1,4, Yi-Lin Cheng1,2, Bi-Hua Ji1,2, Qiao-Yun Fang1,2, Yu-Zhen Li1,2, Fu-Sheng Zhou1,2, Jian-Wen Han1,2, Cheng Quan1,2, Bin Chen1,2, Jian Lin Liu1,2, Da Lin1,2, Li Fan1,2, An-Ping Zhang1,2, Sheng-Xue Liu1,2, Chu-Jun Yang1,2, Pei-Guang Wang1,2, Wen-Ming Zhou1,2, Guo-Shuo Lin1,2, Wei-Dong Wu1,2, Xing Fan1,2, Min Gao1,2, Bao-Qi Yang1,2, Wen-Sheng Lu1,2, Zhang Zhe1,2, Kun-Ju Zhu1,2, Song-Ke Shen1,2, Min Li1,2, Xiao-Yun Zhang1,2, Ting-Ting Cao1,2, Wei Ren1,2, Xin Zhang1,2, Jun He1,2, Xian-Tao Tang1,2, Shun Lu1,2, Jian-Qiang Yang1,2, Lin Zhang1,2, Dan-Ni Wang1,2, Feng Yuan1,2, Xian-Yong Yin1,2, Hong-Jie Huang1,2, Hai-Feng Wang1,2, Xiu-Yi Lin1,2 & Jian-Jun Liu1,2
The Research Relevant to Biobank

Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility

To further understanding of the genetic basis of type 2 diabetes (T2D) susceptibility, we aggregated published meta-analyses of genome-wide association studies (GWAS), including 26,488 cases and 83,964 controls of European, east Asian, south Asian and Mexican and Mexican American ancestry. We observed a significant excess in the directional consistency of T2D risk alleles across ancestry groups, even at SNPs demonstrating only weak evidence of association. By following up the strongest signals of association from the trans-ethnic meta-analysis in an additional 21,491 cases and 55,647 controls of European ancestry, we identified seven new T2D susceptibility loci. Furthermore, we observed considerable improvements in the fine-resolution of common variant association signals at several T2D susceptibility loci. These observations highlight the benefits of trans-ethnic GWAS for the discovery and characterization of complex trait loci and emphasize an exciting opportunity to extend insight into the genetic architecture and pathogenesis of human diseases across populations of diverse ancestry.

Table 3 Properties of the 99% credible sets of SNPs at ten established T2D susceptibility loci

<table>
<thead>
<tr>
<th>Locus</th>
<th>SNP</th>
<th>Ctr</th>
<th>99% credible set: European ancestry meta-analysis</th>
<th>99% credible set: trans-ethnic meta-analysis</th>
<th>99% credible set: reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SNPs</td>
<td>build 36 location (bp)</td>
<td>SNPs</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAZF1</td>
<td>9</td>
<td>75,685</td>
<td>28,147,081-28,222,275</td>
<td>4</td>
<td>15,667</td>
</tr>
<tr>
<td>CDKAL1</td>
<td>15</td>
<td>24,244</td>
<td>20,757,688-20,811,931</td>
<td>2</td>
<td>1,049</td>
</tr>
<tr>
<td>HHELD1</td>
<td>8</td>
<td>10,166</td>
<td>64,452,862-44,473,956</td>
<td>2</td>
<td>937</td>
</tr>
<tr>
<td>ICF2L2</td>
<td>10</td>
<td>3,684</td>
<td>114,776,078-114,757,761</td>
<td>2</td>
<td>2,309</td>
</tr>
<tr>
<td>FTO</td>
<td>21</td>
<td>45,981</td>
<td>52,357,038-52,322,988</td>
<td>10</td>
<td>39,335</td>
</tr>
<tr>
<td>CDK2OA1</td>
<td>9</td>
<td>3</td>
<td>2,019</td>
<td>22,122,076-22,122,076</td>
<td>1</td>
</tr>
<tr>
<td>PPARG</td>
<td>23</td>
<td>765,769</td>
<td>12,106,587-12,131,955</td>
<td>21</td>
<td>265,769</td>
</tr>
</tbody>
</table>

The properties are based on association summary statistics from the meta-analysis of the European ancestry GWAS only (12,171 cases and 56,862 controls) and the trans-ethnic meta-analysis of European, east Asian, south Asian and Mexican and Mexican American ancestry GWAS (26,488 cases and 83,964 controls).
The Research Relevant to Biobank

Molecular diagnosis: Personalized medicine

Fig. 1. *PRKACA* L205R mutations in ACAs and landscape of somatic mutations in cortisol-producing ACTs. Candidate cancer genes (4) are listed vertically on the left. Columns represent samples, with the average mutation rate in exon regions at the top. Samples are arranged from left to right by subtypes and mutation numbers. Histological subtypes and gender of each patient are reported at the bottom (green, ACA; red, AIMAH; orange, ADO; purple, female; blue, male). Colored rectangles indicate mutation category observed in the cohort. Asterisks indicate significantly mutated genes in tumor subtypes (*PRKACA, 28/39 in ACA; DOT1L, 2/7 in AIMAH; CLASP2, 2/3 in ADO).

Activating Hotspot L205R Mutation in *PRKACA* and Adrenal Cushing's Syndrome

Yanan Cao,1† Minghui He,2† Zhibo Gao,2† Ying Peng,1 Yanli Li,1 Lin Li,2 Weiwei Zhou,1 Xiaochun Li,2 Xu Zhong,1 Yiming Lei2, Tingwei Su,1 Hang Wang2, Yiran Jiang,1 Lin Yang,2 Wei Wei,1 Xu Yang,2 Xiuli Jiang,1 Li Liu,2 Juan He,1 Junna Ye,1 Qing Wei,4 Yingrui Li,2 Weiqing Wang,1* Jun Wang,2,5,6,8* Guang Ning1,3,4
The Research Relevant to Biobank

A China case as National Children's Study (NCS) in US

3000 cases

Data management
Independent Ethics Rev.
Third party bio-storage
Project management

259,657 cases

Towards evidence-based public health policy in China

Fan Jiang, Jun Zhang, Xiaoming Shen

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39,938 cases
Thanks!

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