Personalized Medicine: Inclusive New Drug Development Based on Disease Molecular Subtyping (Postprint)

Authors: Shanghai Institute of Materia Medica, Chinese Academy of Sciences

Date: 2017-02-08T00:00:00+00:00

Abstract

Currently, the disease spectrum in China has shifted from infectious diseases to complex diseases as the predominant health challenge. The complex pathogenesis of diseases, substantial individual patient variations, and the lack of personalized drug characteristics for sensitive populations have resulted in low average drug efficacy and enormous wasteful expenditure. The core of the Strategic Priority Program (Category A) of the Chinese Academy of Sciences, "Personalized Medicine—Universal New Drug Research and Development Based on Disease Molecular Typing" (abbreviated as the Personalized Medicine Pilot Program), is to identify sensitive populations for existing drugs to improve efficacy and reduce toxicity; to develop personalized new drugs suitable for large-scale populations targeting sensitive groups, thereby substantially reducing medication waste and lowering treatment costs. The major scientific and technological layout of personalized medicine research represents an important initiative to achieve seamless integration and organic transformation among basic life sciences, drug research and development, and clinical medicine, and is of great significance for China to seize the strategic high ground in precision medicine.

Full Text

Preamble

Strategic Priority Research Program (Category A) of the Chinese Academy of Sciences
ChinaXiv Partner Journal
Personalized Medicine—Affordable New Drug R&D Based on Disease Molecular Classification

1. Background and Significance

The disease spectrum in China has shifted from infectious diseases to complex diseases, posing major challenges to population health and sustainable development. Complex diseases such as cancer, metabolic disorders, autoimmune diseases, and neuropsychiatric conditions exhibit high heterogeneity, with significant individual variation among patients and low average drug efficacy, resulting in substantial waste of medical resources. Traditional drug development models are no longer adequate to address these challenges.

Personalized medicine represents the third wave of drug development, following phenotype-based and genotype-based approaches, and will become the dominant paradigm in international pharmaceutical R&D over the next 10–20 years. The Strategic Priority Research Program (Category A) "Personalized Medicine —Affordable New Drug R&D Based on Disease Molecular Classification" (hereinafter referred to as the Personalized Medicine Program) aims to identify drug-sensitive subpopulations to improve efficacy and reduce toxicity. By developing personalized drugs tailored for these sensitive groups, the program will significantly reduce medication waste and lower treatment costs. This strategic initiative will create seamless integration and organic transformation among basic life sciences, drug discovery, and clinical medicine, positioning China at the forefront of precision medicine.

The program will employ not only traditional life sciences knowledge, methods, and technologies—including molecular, cellular, and structural biology—but also emerging disciplines such as life omics, systems biology, and advanced structural biology to develop new theories, methods, and technologies. These efforts will uncover novel signal transduction pathways, biological networks, and new functions of genes and proteins, thereby enriching our fundamental understanding of life sciences and establishing a strategic technological reserve to transform China' s pharmaceutical innovation landscape.

Focusing on major complex diseases with high incidence in Chinese populations, the program will yield tangible benefits for public health. As socioeconomic development and population aging accelerate, complex diseases have become the primary threats to Chinese citizens. There is an urgent need to create effective, affordable new medicines for these conditions. By targeting cancer, metabolic diseases, autoimmune disorders, and neuropsychiatric diseases, the program will generate novel targets, biomarkers, and high-performance personalized drugs, enabling the right drug for the right patient, improving therapeutic outcomes, reducing adverse effects, and ultimately benefiting the people while alleviating pressure on national healthcare resources.

2. Progress Achieved

Since its launch, the program has established research platforms and technical systems for personalized medicine across oncology, metabolic diseases, neuropsychiatric disorders, and autoimmune diseases. Notably, over 100 patient-derived

xenograft (PDX) models have been developed for liver, gastric, and pancreatic cancers. In terms of personalized drug discovery, the pipeline includes 9 candidate drugs in clinical trials, 1 submitted for clinical investigation, and 22 in preclinical development.

Key achievements include:

Anti-Alzheimer' s candidate drug 971 is currently in Phase III clinical trials. Clinical studies have confirmed its efficacy and unique mechanism of action, validating its A -targeting therapeutic strategy. Using A -PET imaging for sensitive patient screening and efficacy monitoring, the program has identified cerebrospinal fluid A /tau, blood ApoE4, and blood exosomal A /tau as efficacy biomarkers, with FDG-PET imaging to indicate disease progression. This positions 971 as a potentially world-leading, original Chinese personalized medicine for Alzheimer' s disease.

Antidepressant candidate drug 奥生乐赛特 is in Phase II clinical trials.

Five oncology candidates are in Phase I trials: the multi-target receptor tyrosine kinase inhibitor AL3810 (targeting FGFR/VEGFR/PDGFR), the novel camptothecin derivative 盐酸希明替康, the second-generation ALK inhibitor 丁二酸复瑞替尼 SAF-189s, the novel PARP1 inhibitor 希明哌瑞, and the refractory/relapsed multiple myeloma inhibitor 倍赛诺他.

Additional candidates include the systemic lupus erythematosus treatment 马来酸蒿乙醚胺 (SM934) in Phase I, the pulmonary arterial hypertension drug TPN171 in Phase I, and the c-Met inhibitor 谷美替尼 (SCC244) submitted for clinical investigation. Furthermore, 10 oncology candidates, 1 autoimmune disease candidate, 6 metabolic disease candidates, and 5 neuropsychiatric candidates are in preclinical development.

The program has also made significant progress in biomarker discovery:

(1) Biomarkers for anticancer drug efficacy and toxicity: Gastric, thyroid, and liver cancers have been identified as sensitive tumor types for AL3810. In nearly 40 gastric cancer models, sensitive populations have been characterized and several sensitivity-related genes identified, with functional validation underway. A mouse model for 盐酸希明替康-induced diarrhea has been established, revealing immune response pathways involved in this toxicity and identifying a potential toxicity biomarker currently undergoing clinical sample validation. In ALK fusion-driven tumors, apoptosis has been identified as the core cellular event underlying the efficacy of 丁二酸复瑞替尼, with one downstream key protein identified as a potential efficacy monitoring biomarker. For 谷美替尼, G1/S cell cycle arrest has been identified as the core cellular event, with c-Myc downregulation as the key molecular event, validated in animal models as a potential efficacy biomarker.

(2) Novel mechanisms and target discoveries: The program has revealed, for the first time, that feedback activation of leukemia inhibitory factor receptor (LIFR) causes resistance to HDAC inhibitors in solid tumors, discovering

a mechanism-based combination therapy strategy with broad implications for HDAC inhibitor applications. Targeting SPOP protein-protein interactions, the program has obtained small molecules that bind SPOP by leveraging structural features from SPOP-substrate peptide complex crystal structures and applying structure-based virtual screening and medicinal chemistry optimization. This work provides pharmacological validation of SPOP as a drug target for clear cell renal carcinoma and opens a new direction distinct from kinase inhibitors for renal cancer therapy.

3. Innovation and Uniqueness

The program addresses critical scientific questions regarding complex disease mechanisms, individual patient variation, drug sensitivity mechanisms, and personalized treatment paradigms. Focusing on highly prevalent, heterogeneous, and harmful complex diseases in Chinese populations, the program employs a "patient stratification, drug layering" approach through biomarker and target discovery to enable personalized use of existing drugs and develop novel personalized medicines. Key innovations include:

(1) Research Strategy: Systematic, large-scale personalized drug R&D for malignant tumors, autoimmune diseases, Type II diabetes, and neuropsychiatric disorders in Chinese populations, creating a demonstrable and replicable model.

(2) Technology Integration: Integration of deep sequencing, disease omics, big data mining, large-scale cell culture, and personalized drug screening and design technologies.

(3) Organizational Model: Disease-centered scientific layout with seamless integration of basic life sciences, pharmaceutical research, and clinical medicine, enriching translational medicine.

(4) Establishment of an International "Personalized Medicine Research Center" : Construction of key resource repositories and information sharing systems, integrating complete "clinical-basic research-drug development" resources and data to sustain personalized medicine research.

4. Significance for Industry

The personalized drug R&D model established by this program represents the future paradigm for international pharmaceutical development over the next 10–20 years. The program will build core resource systems including clinical tumor biobanks, PDX models, patient-derived cells (PDC), diabetic patient biobanks, and information databases encompassing molecular classification, genetic information, omics data, biomarkers, targets, and drug interaction profiles for Chinese populations with liver cancer, gastric cancer, and diabetes. This will consolidate talent, achievements, and resources generated during the program, prevent fragmentation of scientific resources, and ensure sustainable development of personalized medicine research.

5. Recommendations for Future Development

Personalized medicine R&D aligns with precision medicine principles and will be widely adopted in the future. Future development should emphasize:

(1) Deepening the precision treatment concept: Focus on the seamless integration of complex disease biomarkers, new drug R&D, and clinical application through multidisciplinary collaboration. This extends upstream to enhance basic life science research and downstream to improve drug development capabilities, breaking down barriers between basic biology, medicine, drug discovery, and clinical practice. The bidirectional, open "from bench to bedside and back" model will pioneer a direct path from basic research to clinical application, leading transformative innovation in China' s drug development.

(2) Building the "Personalized Medicine Research Center" : Establish core resource systems including clinical tumor samples, PDX models, PDCs, and diabetic patient samples, along with information systems for molecular classification and biomarker discovery. This will preserve and consolidate program outcomes for sustainable research.

(3) Reforming personalized drug regulatory policies: Personalized drug research requires close alignment with clinical studies and regulatory policies. Enhanced communication with regulatory agencies and policy research are needed to explore new approval criteria for personalized medicines, accelerating translation of research findings to clinical practice.

The Personalized Medicine Program represents a forward-looking, strategic S&T layout by the Chinese Academy of Sciences, addressing world-class scientific frontiers, national economic needs, and major strategic demands. It targets complex diseases prevalent in Chinese populations through synergistic collaboration across life sciences, pharmaceutical sciences, and clinical research. The program' s design, objectives, methodology, team, and resources demonstrate international competitiveness and feasibility.

CAS has consistently played a core, leading role in national innovative drug R&D, with deep expertise in disease molecular mechanisms, biomarker discovery, and platform construction. Mobilizing these strengths and leveraging national resources such as the National Compound Library, clinical tissue biobanks, and databases will create powerful competitive advantages.

The program meets the requirements for Category A Strategic Priority Research Programs by addressing major public welfare and core technological challenges. It capitalizes on the third wave of drug development opportunities, synchronizing with developed nations in this new paradigm. By integrating basic life science research with clinical practice, combining drug discovery with cutting-edge theories and methods, and linking new drug discovery with repositioning of existing drugs, the program aligns with the mission to "promote technologi-

cal transformation and emerging industry development, serving sustainable economic and social development." It will make significant contributions to achieving critical drug development goals and driving national economic and social progress.

Host Institution: Shanghai Institute of Materia Medica, Chinese Academy of Sciences

Personalized medicine research represents an international frontier and hotly competitive field. While the US government and NIH have prioritized "precision medicine" in funding, this program' s focus on Chinese populations and integration of domestic research strengths positions China to compete globally. The program' s outputs will help relieve healthcare cost pressures and provide affordable, effective medicines for the population.

Expert Evaluations:

Wang Xiaofan, Tenured Professor at Duke University Medical Center and President of the Society of Chinese Bioscientists in America, notes that the program' s focus on Chinese complex diseases through coordinated life science, pharmaceutical, and clinical research demonstrates international competitiveness. CAS' s deep accumulation in disease molecular mechanisms and biomarker discovery provides a strong foundation.

Wang Shaomeng, Professor of Medicine, Pharmacology and Medicinal Chemistry at the University of Michigan and Director of the Center for Therapeutic Innovation, emphasizes that personalized medicine R&D requires integration of basic research and clinical practice. The program' s establishment of a dedicated research center and resource systems will consolidate achievements and ensure sustainable development. Reforming regulatory policies to create new approval pathways for personalized medicines is essential for accelerating clinical translation.

Note: Figure translations are in progress. See original paper for figures.