Frontier Interdisciplinary Strategy

Strategic Research on The Metabolic Biology

Strategic Research on the Metabolic Biology Research Team

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Report Writing Group

Editorial team leader:

Bao-Liang Song	Wuhan University

Editorial team members:

Xiong-Jie Shi	Wuhan University
Chenqi Xu	Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences
Xiaoying Li	Fudan University
Jia Li	Shanghai Institute of Materia Medica, Chinese Academy of Sciences
Ru Wang	Shanghai University of Sport
Zhihua Liu	Tsinghua University
Daoxin Xie	Tsinghua University
Jianbin Yan	Agricultural Genomics Institute at Shenzhen, Chinese Academy of Agricultural Sciences
Jie Luo	Hainan University
Tiangang Liu	Shanghai Jiao Tong University
Dayong Yang	Fudan University
Xuefeng Lu	Qingdao Institute of Bioenergy and Bioprocess Technology, Chinese Academy of Sciences
Ertao Wang	Institute of Plant Physiology and Ecology, Chinese Academy of Sciences
Xin Zhou	Innovation Academy for Precision Measurement Science and Technology, Chinese Academy of Sciences
Zheng-Jiang Zhu	Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
Jianfei Lai	Wuhan University
Yan Wang	Wuhan University

Abstract

Metabolic biology represents a cutting-edge interdisciplinary field that integrates biochemistry, physiology, genetics, medicine, and other domains, aimed at elucidating the core metabolic mechanisms underlying life activities, the patterns of metabolic changes under physiological and pathological conditions, and the interactions between organisms and their environment. With the advancement of genomics, proteomics, metabolomics, and related technologies, research achievements in this field have grown substantially, expanding from traditional biology and medicine to encompass chemistry, food science, environmental science, agriculture, forestry, fisheries, and engineering sectors, demonstrating remarkable interdisciplinary characteristics and application potential. China has emerged as one of the core research forces in this field and exhibits tremendous development potential. Research in this domain holds significant strategic importance for addressing major challenges in human health, food security, energy, and environmental sustainability.

Currently, metabolic biology research focuses on several key areas. In "Metabolism and Disease," emphasis is placed on elucidating the molecular mechanisms of metabolic disorders (such as obesity, diabetes, and cardiovascular diseases), identifying genetic susceptibility genes and key regulatory targets, and developing novel diagnostic and therapeutic strategies. The core of "Metabolism and Drug Development" lies in strengthening fundamental research "from zero to one," discovering new targets, understanding common pathological mechanisms of metabolic disorders in major chronic diseases, and advancing innovative drug development. Additionally, research encompasses "Metabolism and Proactive Health," exploring molecular mechanisms of lifestyle interventions; "Human Symbiotic Microbial Metabolism," analyzing microbe-host metabolic network interactions; "Metabolism and Agriculture," improving crop metabolism to enhance yield and stress resistance; "Metabolism and Synthetic Biology," designing and engineering microorganisms for efficient production of valuable compounds; "Metabolism and Biomaterials," optimizing biocompatibility of biological materials; "Metabolism and Biomass Energy" as well as "Metabolism and Carbon

Neutrality," utilizing metabolic engineering to promote renewable energy production and CO_2 biological fixation; and "New Technology Development and Metabolomics," advancing high-sensitivity, high-throughput analytical technologies.

To drive the strategic development of metabolic biology in China, it is recommended that the national level strengthen top-level design and resource integration, establish a key special program for metabolic biology, and construct a National Center for Metabolic Biology Science and Technology or National Key Laboratories. The key special program shall support exploration of major scientific questions and breakthrough of critical technologies through multi-dimensional strategies, facilitating the integration of basic research with industrial applications. The national-level platforms are committed to establishing advanced instrument-sharing platforms, building national-level metabolic disease resource banks and distinctive natural product libraries, developing artificial intelligence systems for metabolic network analysis, cultivating high-level talent, and addressing bottleneck issues in key detection instruments and databases. Through these initiatives, China's original innovation capacity in metabolic biology research will be enhanced, the healthy development of related industries will be promoted, and robust support will be provided for national health and economic development.

Content

Chapter 1 Overview of Metabolic Biology

Metabolism refers to a series of orderly chemical reactions occurring within living organisms to sustain life activities. It is the core and foundation of all biological processes. Metabolic biology is an interdisciplinary field that integrates biochemistry, physiology, pathology, pharmacology, new drug development, microbiology, zoology, botany, genetics, synthetic biology, and bioinformatics. Metabolic biology elucidates the basic mechanisms of metabolism, clarifies the characteristics of metabolic changes under physiological and pathological conditions, discovers the laws of interaction between organisms and the environment, and facilitates their transformation and utilization. In recent years, the rapid development of genomics, proteomics, metabolomics, and related technologies has propelled life sciences into the era of big data.

Over the past decade, research in metabolic biology has exhibited an upward trend both domestically and internationally. Particularly in the last five years, research outputs have grown significantly, indicating that metabolic biology is in a distinct period of ascent and development, characterized by the following features: First, research has broken through the traditional disciplines of biology, medicine, and pharmaceutics, and has extensively expanded to multiple disciplines such as chemistry, food science, and environmental science, as well as multiple industries including agriculture, forestry, fishery, and engineering. Second, research methods and results demonstrate increasing interdisciplinarity and strong pertinence, and are combined with industrial applications. Third, Chinese universities and research institutes have simultaneously exerted efforts and achieved considerable accomplishments in this field. At present, China and developed countries in Europe and America have become the core forces in this research field. China is currently in a period of rapid growth in research and exhibits enormous potential for development in this field.

To better focus and plan the future development of metabolic science in China, this strategic research report investigates the research status in China and internationally in ten areas: metabolism and disease, metabolism and new drug development, metabolism and proactive health, metabolism of human commensal microorganisms, metabolism and agriculture, metabolism and microbial engineering, synthetic biology, metabolism and biomaterials, metabolism and biomass energy, metabolism and carbon neutrality, carbon peaking, new technology development, and metabolomics. The report summarizes key scientific and technological issues, refines development ideas and policy recommendations in related fields, and promotes the rapid development of basic scientific research and related application industries in the field of metabolism.

Chapter 2 The Main Content, Current Status, and Key Scientific Issues of Metabolic Biology

2.1 Metabolism and Disease

2.1.1 Strategic Value

With China's economic growth, changing lifestyles, and an aging population, the incidence of metabolic diseases such as obesity, diabetes, non-alcoholic fatty liver disease, and cardiovascular and cerebrovascular diseases has been increasing year by year. These diseases have become major public health problems that seriously threaten the health of Chinese citizens and greatly increase the socioeconomic burden. Currently, China has approximately 330 million patients with cardiovascular diseases, 200 million patients with fatty liver, and 130 million patients with diabetes. In addition, 10.9 million men and 49.3 million women in China suffer from osteoporosis. Apart from their own harms, the aforementioned metabolic diseases are often closely related to tumors, neurodegenerative diseases, cognitive disorders, and immunological diseases, severely affecting patients' quality of life.

Metabolic disorders are a common pathological mechanism underlying these complex diseases. Insufficient understanding of the common pathological mechanisms of metabolic disorders is the main bottleneck restricting the development of original new drugs. Therefore, studying the genetic and microenvironmental factors involved in the occurrence of metabolic disorders during disease development, investigating and elucidating cellular metabolism and its interaction with the microenvironment at both micro and macro levels, as well as the interaction and regulation between different metabolic organs, and clarifying the key molecular mechanisms and regulatory networks of metabolic disorders will help reveal the pathological regulatory mechanisms of diseases and identify original metabolic regulatory targets. This will provide strong evidence for the development of drug targets and prevention and control strategies for metabolic diseases. Improving the prevention and treatment of metabolic diseases can not only improve national health but also effectively reduce national medical expenditure and economic burden, which has important scientific research value and strategic significance. This is also highly consistent with the "Healthy China 2030" plan outline issued by the Central Committee of the Communist Party of China and the State Council.

2.1.2 Critical Scientific and Technical Issues:

(1) How to identify the genetic susceptibility genes and key regulatory genes for metabolic diseases?

(2) How to detect the heterogeneity of cellular metabolism in the metabolic tissue microenvironment during disease occurrence and development?

(3) How to identify specific metabolites for metabolic diseases and identify potential drug targets and diagnostic and therapeutic technologies?

(4) How to establish a large-scale high-throughput organ analysis platform covering population genetic variations and human metabolic characteristics?

2.1.3 Research Foundation and Conditions in China and Internationally

A century ago, it was discovered that metabolic imbalances and disorders are commonly present in various pathological processes. Changes in environmental factors reshape the body's metabolic network, affecting immune/inflammatory status, insulin sensitivity, gut microbiota stability, etc., leading to metabolic imbalances and disorders, triggering metabolic diseases. Various treatment strategies have been developed for metabolic diseases targeting nutrient intake imbalances, metabolic pathway remodeling, changes in metabolite-driven gene expression regulation, and alterations in the microenvironment composition: (1) Regulating nutrient intake, such as targeting SGLT2 inhibitors and GLUT1 inhibitors or ASCT2 antagonists for diabetes and anti-tumor treatment, respectively; (2) Regulating nutrient metabolism, such as the activation of oncogenes in tumor cells that increase the expression of glycolytic pathway metabolic enzymes, which can serve as targets for tumor therapy; (3) Modulating the content of cell metabolites affecting cellular epigenetics, such as acetyl-CoA and S-adenosylmethionine participating in acetylation and methylation, and α-KG participating in DNA demethylation.

However, most research on metabolic diseases (such as diabetes, obesity, fatty liver, cardiovascular diseases, etc.) is still at a simple genetic correlation level, without in-depth exploration of the physiological, pathological, and pharmacological biology of the body. Body metabolism requires the coordinated operation of multiple organs and tissues; therefore, research on metabolic diseases cannot be limited to isolated organs but should focus on the metabolic interactions between cells and the microenvironment, the microenvironment and tissues/organs, and the organs. Through the establishment of in vivo metabolic tracing systems, such as isotope tracing combined with two-dimensional imaging, multi-omics, and other technologies, the metabolic characteristics of diseased organs can be studied at the spatial level, which is crucial for discovering new metabolic regulatory targets and proposing original theories in the future.

2.2 Metabolism and New Drug Research and Development

2.2.1 Strategic Value

The life expectancy of our nation's population has increased by 18 years compared to 1970. It is projected that from 2010 to 2040, the proportion of our country's population aged 60 and above will increase from 12.4% (168 million) to 28% (402 million), transitioning from mild to severe population aging. With the exacerbation of an aging society, the prevalence of various chronic diseases has increased significantly, such as diabetes, non-alcoholic fatty liver disease, cardiovascular diseases, organ fibrosis, autoimmune diseases, neurological diseases, and tumors, among other major chronic diseases. On one hand, these pose a tremendous threat to the health and lives of our citizens, and on the other hand, they also impose a heavy burden on the national economy. In recent decades, domestic new drug research has developed rapidly, but it still cannot meet the health needs of our citizens, urgently requiring a strong push for new drug research and development. Currently, our country has become the second-largest pharmaceutical market globally, second only to the United States. However, among the drugs produced in our country, generic drugs account for 95%. Most of the new drugs developed in our country are still follow-ups to existing new drugs from abroad, primarily rapid imitations of innovative varieties. The development of new drugs with novel mechanisms of action and the original new drugs based on them are essentially absent. The national "14th Five-Year Plan" puts forward new requirements for the development of science and technology, emphasizing "four orientations." Innovative drug research and development is at the forefront of world science and technology, a major national need, and an important guarantee for people's health and lives, which can no longer be delayed.

2.2.2 Critical Scientific and Technical Issues:

(1) How to strengthen basic research "from 0 to 1," open up new fields, propose new theories, develop new methods, and discover and propose new drug targets in this process?

(2) How does metabolic disorder, as a common pathological mechanism, affect the occurrence and development of major chronic diseases such as metabolic diseases, cardiovascular diseases, autoimmune diseases, neurological diseases, and tumors, and how does an in-depth understanding of its mechanism become a key scientific issue for innovative drug research and development?

(3) How to strengthen the development of drugs targeting metabolic disorder regulation through in-depth research on disease mechanisms and precise drug design, and develop targeted drugs with better efficacy and lower side effects?

(4) What are the application prospects of new therapies such as protein and peptide drugs, antibody drugs, small nucleic acid drugs, mRNA drugs, vaccines, cell therapy, gene therapy, gene editing, xenotransplantation, and microbial therapy in metabolic diseases, and how to strengthen the research and development, risk assessment, and prevention and control of these new therapies?

2.2.3 Research Foundation and Conditions in China and Internationally

Metabolic dysfunction can lead to various diseases, including obesity, diabetes, and hypertension, and increase the risk of depression, dementia, and Alzheimer's disease. Metabolic reprogramming is also a pathogenic factor for tumors and immune diseases. Therefore, targeting metabolic disorders may be a potentially effective treatment strategy. In 2022, the U.S. Food and Drug Administration (FDA) approved a total of 37 new drugs, of which 5 targeted metabolic regulation, mostly for the treatment of rare diseases. In 2022, China approved 18 new domestic drugs, with only 1 targeting metabolic regulation. Targeting metabolic regulation has made some progress in the field of rare diseases, but it is still relatively lacking in the treatment of major chronic diseases.

Drug targets are biological macromolecules associated with disease processes and can be acted upon by drugs. Metabolic enzymes and receptors are the main targets of metabolic regulation, but their roles in diseases are still unclear. The pathological mechanisms of metabolic disorder-related diseases need to be thoroughly studied, with emphasis on original theoretical and technological breakthroughs and the discovery of new drug targets. The confirmation of new targets often gives rise to "blockbuster" drugs. For example, atorvastatin, which targets HMG-CoA reductase, had peak annual sales of $12.8 billion and was the first "blockbuster drug" with over $10 billion in sales. In addition, the key secretory protein PCSK9, which regulates cholesterol absorption and metabolism, was discovered in 2003 and was simultaneously proven to significantly lower low-density lipoprotein cholesterol levels. Related drugs were approved for marketing by the FDA and the European Medicines Agency (EMA) in 2017, with annual sales of around $1 billion. Moreover, while there is intense competition for therapeutic antibody drugs, siRNA drugs also started their era in the early 20th century. An siRNA drug targeting PCSK9 developed by Novartis was approved in Europe in December 2020 and landed in Boao, Hainan, China in 2021.

2.3 Metabolism and Active Health

2.3.1 Strategic Value

Active health is an original concept proposed by China in the field of health, which first officially appeared in the "13th Five-Year Plan for Health and Health Science and Technology Innovation" jointly issued by the Ministry of Science and Technology and other departments in 2017. In 2022, the development of new active health technologies and models was included as one of the six major strategic tasks in the "14th Five-Year Plan for Health and Health Science and Technology Innovation."

(1) Active health is an effective means to ensure people's life and health: With the continuous expansion of the population with metabolic diseases and the ongoing exacerbation of an aging society, traditional medical and health services cannot meet the increasing health needs of the people. Lifestyle interventions such as exercise, nutrition, and sleep are essential components of active health. Research has confirmed that regular exercise can reduce disease risk factors, lower the risk of type 2 diabetes, cardiovascular diseases, and metabolic syndrome by 41% to 59%, and decrease the risk of all-cause mortality and cardiovascular disease mortality by 30% to 45%. Reasonable dietary patterns, such as low-insulin diets, low-inflammatory diets, and diabetes risk reduction diets, can significantly reduce the risk of type 2 diabetes by 44% to 65% and the risk of cardiovascular diseases by 27% to 32%.

(2) Active health is an inevitable requirement for promoting the construction of a healthy China: The Healthy China strategy focuses on two key points: the entire population and the whole life cycle. It takes people's health as the center, emphasizes prevention, and promotes a healthy lifestyle, giving rise to active health. Active health emphasizes the shift from "disease-centered" to "health-centered," advocates that each person is the primary responsible party for their own health, and enhances the body's ability to prevent and resist diseases through lifestyle interventions such as exercise and nutrition.

(3) Active health is a key measure to achieve the development of the health industry: Currently, China's health industry shows a trend of cross-integration and development. New forms of health and medical services, such as health consultation and wellness services, have taken shape, and the total scale of the health service industry is expected

to reach 16 trillion yuan by 2030. Under the active health model, innovations in technologies such as exercise health promotion and precise nutrition regulation, as well as the development of wearable health monitoring devices, health risk early warning models, and intelligent rehabilitation aids, are expected to become new economic growth points for the health industry.

2.3.2 Critical Scientific and Technical Issues:

(1) What are the molecular mechanisms of exercise, fasting, sleep, and psychology in promoting human health? For example, which key response factors and signaling pathways play a decisive role in promoting metabolic homeostasis? Can a map of biomolecular reactions induced by exercise, fasting, sleep, and psychology be drawn? What are the mechanisms of interactive dialogue between various organs?

(2) What kind of "dose-effect" relationship can define the safety and effectiveness of exercise, fasting, sleep, and psychology in improving chronic diseases? How to design a precise exercise plan for chronic disease improvement that is both safe and effective?

(3) How to innovate tracing technologies to explore the metabolic pathways of substances such as sugar, fat, and protein during different behavioral patterns? What are the temporal and adaptive change characteristics of these metabolic processes?

(4) How to use multi-source intelligent wearable devices to collaboratively perceive and quickly and accurately measure and analyze metabolic changes under different behavioral patterns? Based on these factors, can a precise evaluation system be established?

(5) How can modern information technology and artificial intelligence assist in the above research?

2.3.3 Research Foundation and Conditions in China and Internationally

In 1968, Kenneth H. Cooper, a pioneer in the integration of sports and medicine, first proposed that "exercise is medicine," which has now spread globally, and a large amount of human and financial resources have been invested in related research. Diet plays a key role in regulating metabolism, and fasting can regulate metabolism and prolong life. Proper sleep also has a huge impact on the occurrence of cardiovascular diseases and Alzheimer's disease. Physical exercise combined with fasting can better improve aging and metabolism-related diseases. In 2016, the National Institutes of Health (NIH) in the United States invested 170 million US dollars to establish five centers, bringing together several world-renowned universities and research institutions, including Stanford University and Mayo Clinic, to collaboratively tackle the mechanisms of exercise and fasting in improving aging and metabolism-related diseases. In 2012, China introduced the concept of "exercise is medicine" from the American College of Sports Medicine and proposed the guideline of "integration of sports and medicine." Over the years, sports science has actively explored and researched the combination of sports and medicine. For example, the team led by Wang Ru from Shanghai University of Sport systematically summarized the exercise and dietary intervention methods for 26 different diseases and revealed the potential mechanism of exercise alleviating diabetes mediated by the gut microbiota based on a cohort of thousands of athletes. The team led by Li Liming from Peking University found through a 10-year follow-up of more than 460,000 adults that active participation in physical activity may help prevent hepatobiliary diseases. The team led by Gao Feng from the Fourth Military Medical University studied the cardioprotective effect of circulating exosomal microRNA derived from volunteers after long-term exercise. However, systematic and targeted implementation rules for the integration of sports and medicine, as well as supporting policies and regulations, have not yet been issued, making it difficult to operate and comprehensively promote the integration of sports and medicine in practice, and limited resources cannot achieve precise investment and optimal allocation. In the past three years, China has funded 69 related projects, while the NIH in the United States has funded 573 related projects, with a funding intensity far higher than that of China, which may be one of the reasons why China's research level in this field currently lags behind developed countries such as the United States.

2.4 Metabolism of Human Commensal Microorganisms

2.4.1 Strategic Value

Microorganisms are closely related to human health. Pathogenic microorganisms remain one of the most significant threats to public health, while the emerging microbiome has a profound impact on human health. Infectious diseases caused by pathogenic microorganisms such as viruses, bacteria, fungi, and parasites result in over 10 million deaths annually, accounting for approximately one-fifth of the total global deaths each year. From the Spanish flu virus a century ago to the unresolved challenges of tuberculosis, malaria, AIDS, hepatitis B, and others, they constantly test the global public health system. China has a large population and relatively underdeveloped medical and health conditions. Coupled with the high mutation frequency of viral pathogens, the increasingly severe bacterial resistance, and the lengthy drug development cycle, infectious diseases cause a severe social burden in China every year and may potentially become another "bottleneck" area for the country. Therefore, in-depth research on pathogenic microorganisms has extremely far-reaching strategic value for China's biosecurity, social stability, and national economy.

The microbiome refers to the collection of microbial communities and their genetic information in a specific ecological environment. In the past decade, microbiome-related research has received significant attention. The United States, the European Union, and others have successively introduced multiple scientific and technological plans to support microbiome research. Among them, the study of the human microbiome, with the gut microbiome as a typical representative, is a hot topic in current international biomedical research. The microbiome, as the second human genome, possesses enormous metabolic potential and is intertwined with the host's metabolism. Numerous studies have confirmed a strong correlation between the gut microbiome and human metabolic diseases. Additionally, the relationships between pathogenic microorganisms, commensal microorganisms, and host health are complex. Infectious diseases depend on the metabolic adaptation of pathogenic microorganisms and the host's metabolic and immune responses, while the gut microbiome is interconnected with host metabolism, influencing the development of various diseases, including metabolic disorders. Systematically analyzing the associations and mechanisms of the microbe-host metabolic network is of great significance for advancing basic scientific research and medical translational industry, reducing disease burden and medical costs, and improving people's health.

2.4.2 Critical Scientific and Technical Issues:

(1) What are the metabolic regulation mechanisms between pathogenic microorganisms and the host?

(2) How do pathogens and hosts mutually regulate metabolic processes, thereby affecting the occurrence and development of infectious diseases?

(3) What are the modes and metabolic-immune regulatory mechanisms by which the human microbiota influences host metabolism?

(4) How do the human microbiota and their metabolites regulate the occurrence and development of metabolic diseases?

2.4.3 Research Foundation and Conditions in China and Internationally

In recent years, developed countries, mainly in Europe and the United States, have made scientific breakthroughs worth learning from in the field of pathogenic microorganism-host metabolic interactions. Various tissues and cells of the host undergo a series of metabolic changes during infection, which can have either positive or negative effects on the host. Under the inflammatory influence of infection, host cells can alter cholesterol metabolism in the cell membrane and enhance glycolysis. The host limits trace elements through multiple pathways to counteract pathogenic microbial infections. The competition between pathogenic bacteria and the host for the trace element iron even becomes a determining factor in the course of infection. During the infection process, energy is crucial for both the host and the pathogen. Multiple tissues of the host collaboratively maintain blood glucose balance, enhancing the host's tolerance to sepsis. Additionally, some pathogens adapt to the host's metabolism by downregulating the expression of their virulence factors, increasing the host's tolerance to infection. High-throughput metabolomics has revealed that changes in metabolic molecules during the infection process are closely related to the severity of COVID-19 infection. Therefore, tolerating infectious diseases through metabolic regulation has become an exciting emerging research field.

Through years of effort, domestic researchers have made significant progress in the field of infectious diseases, gradually transitioning from epidemiological surveillance, resistance screening, and clinical strain resource integration to advanced technological directions such as molecular epidemiology, pathogenesis, anti-infective immunology, and the development of new vaccines/drugs. The successful development of domestic vaccines and high-affinity antibodies against SARS-CoV-2 fully demonstrates the rapid progress of China's independent research capabilities. However, China is still relatively lagging in the field of pathogen-host metabolic interactions. Chinese scientists have discovered the key metabolic regulatory factor MetR in the nasal colonization of Streptococcus pneumoniae; they have found that Streptococcus pneumoniae regulates the phase variation of its cell wall in response to different physiological environments within the host. Chinese research teams have continuously focused on the renal metabolic indicators of COVID-19 patients, providing a reference for preventive treatment of acute kidney injury in COVID-19 survivors. The above representative research achievements have laid a certain foundation for China's prevention and control of infectious diseases and opened up new directions.

Through years of effort, Chinese scientists have also made gratifying achievements in the study of gut microbiota and metabolic diseases. Research has found that a combination of various dietary fibers promotes the enrichment of short-chain fatty acid-producing gut bacteria, thereby improving type 2 diabetes. Parabacteroides contributes positively to weight loss in patients after sleeve gastrectomy by reducing glutamate. Ethanol produced by gut microbes induces the occurrence and development of fatty liver disease. The secondary bile acid GDCA activates the TGR5 receptor, promoting the secretion of IL-22 by type 3 innate lymphoid cells in the gut, improving polycystic ovary syndrome; the bile acid GUDCA inhibits intestinal epithelial FXR, reduces ceramide production, and improves metabolic diseases; the porcine bile acid HCA targets intestinal FXR and TGR5, promoting GLP-1 secretion and improving glucose homeostasis. The host intestinal epithelial HIF-2α aggravates obesity-related metabolic diseases by inducing an imbalance between Bacteroides vulgatus and Ruminococcus gnavus in the gut, lowering bile acid levels, and inhibiting white adipose tissue browning; Bacteroides xylanisolvens can efficiently degrade intestinal nicotine, thereby improving metabolic diseases; peptidoglycan components regulate insulin secretion and blood glucose balance in pancreatic β cells and promote adrenaline secretion in adrenal chromaffin cells to regulate stress responses. The series of research work by Chinese scientists has revealed new paradigms of gut microbiota-host metabolic interactions, providing new directions and strategies for the prevention and treatment of metabolic diseases.

2.5 Metabolism and Agriculture

2.5.1 Strategic Value

The metabolic products of plants are of great significance to plant growth, development, and stress response, while also providing important material sources for human nutrition and health. As the material basis for crop yield, resistance, and quality, metabolites are crucial to food security and farmers' economic benefits. Research on metabolic biology is an important aspect of realizing the goal set in the report of the 20th National Congress of the Communist Party of China, which is to "ensure that Chinese people hold their rice bowls firmly in their own hands." Research on crop metabolic biology will play a vital role in ensuring high and stable crop yields and improving agricultural economic benefits, and it is also an important embodiment of the concepts of "sustainable development" and "respecting nature, following nature, and protecting nature."

With the rapid development of China's economy and the gradual improvement of people's living standards, food consumption has shifted from "eating enough" to "eating well," and the demand for crop products with high nutritional and health-promoting components has been increasing. According to a report by the World Health Organization, the proportion of the "sub-healthy" population in China has reached 70%. Nutrients derived from crops are an important source of a healthy human diet, and increasing the content of nutritional metabolites in crops is the most economical and efficient way to improve the health of the entire population and solve the "hidden hunger" crisis from the source. At the same time, natural products derived from medicinal plants also play an indispensable role in ensuring the health of the population. Especially during the COVID-19 pandemic, medicinal plants, including traditional Chinese medicinal materials, have received further attention as an important source and guarantee of medicine and health care.

In summary, plant metabolic biology is of great significance for ensuring national food security, biosecurity, and ecological security, improving national nutrition and health, promoting agricultural and rural modernization, and sustainable high-quality development of the national economy.

2.5.2 Critical Scientific and Technical Issues:

(1) How to decipher important metabolic pathways in plants?

(2) How do plants reprogram their metabolism during development and stress response?

(3) How does natural variation in plant metabolic diversity occur, and what is its evolutionary pattern?

(4) What are the physiological roles and mechanisms of metabolites in the plant functional metabolome?

(5) How to identify plant metabolites using high-throughput, high-sensitivity, and high spatiotemporal resolution technologies, and establish a shared metabolite database?

2.5.3 Research Foundation and Conditions in China and Internationally

The analysis and utilization of metabolite synthesis, modification, degradation, transport, and regulation have always been at the forefront and hotspots of plant metabolic biology, while metabolic engineering and synthetic biotechnology involving the efficient biomanufacturing of plant natural products are technological heights that countries around the world are vying for.

In recent years, with the development of omics technologies such as genomics and metabolomics, plant metabolic biology has further developed in terms of research depth and breadth, and research teams in China and internationally have made major scientific breakthroughs in multiple fields. In terms of deciphering the synthesis pathways of important metabolic products in crops, Chinese teams have identified major genes controlling rice nutritional quality and stress physiology, and cloned and identified major genes related to biotic and abiotic stress resistance pathways in rice and their roles in environmental adaptation; Chinese and Israeli teams have respectively analyzed the synthesis and regulation pathways of bitter substances in cucumber and tomato, laying the foundation for further breeding improvement; a British research team systematically analyzed plant triterpene biosynthetic gene clusters, revealing the mechanism by which plants use triterpenes to regulate soil microorganisms; Chinese research teams have deeply analyzed the biosynthetic pathway and regulatory mechanism of cotton phenols, and created seed-specific low-phenol transgenic cotton materials, laying the foundation for comprehensively deciphering the biosynthetic pathway of cotton phenols. At the same time, in terms of deciphering the biosynthetic pathways of plant natural products, Chinese and German research teams have successively reported the missing genes in the biosynthetic pathway of the anticancer star molecule taxol in Taxus, opening up the biosynthetic pathway of taxol and laying the foundation for the low-cost biosynthesis of taxol; American and Chinese research teams have respectively analyzed key genes in the synthesis pathway of hyoscyamine/scopolamine, and realized the heterologous synthesis of scopolamine in microorganisms; a British research team elucidated the biosynthetic pathway of the saponin adjuvant from Quillaja saponaria, making it possible to produce vaccine adjuvants using synthetic biology, and opening up new avenues for obtaining and designing natural and new natural immune stimulants; a German research team deeply analyzed the biosynthetic pathway of vinblastine, and made major progress in using plant and microbial chassis for production; an American research team analyzed the biosynthetic pathway of diosgenin, laying the foundation for the large-scale synthesis of steroid compounds.

On the basis of in-depth analysis of plant metabolite biosynthetic pathways and regulatory networks, research teams at home and abroad have further utilized transgenic and gene editing technologies to create new materials and varieties with enhanced nutrition. For example, a tomato variety rich in γ-aminobutyric acid created by Japanese scientists was approved for market release by the Japanese government, becoming the world's first genetically edited food to be marketed; an American research team achieved simultaneous enhancement of vitamin A and vitamin E synthesis in soybean, and the purple tomato variety they created with high anthocyanin content was approved for market release by the United States Department of Agriculture (USDA); a Belgian team created potatoes rich in folic acid by enhancing the expression of folic acid synthesis genes; a British research team created tomato germplasm with increased vitamin D and dopamine content based on metabolic regulation theory; and Chinese teams have also created a series of new materials and varieties with enhanced flavor and nutrition, such as rice with high folic acid, thiamine, anthocyanin, and astaxanthin content in the grain, and tomatoes with high vitamin D, γ-aminobutyric acid, anthocyanin, and carotenoid content in the fruit.

2.6 Metabolism and Synthetic Biology

2.6.1 Strategic Value

Microbial engineering and synthetic biology constitute an applied discipline that aims to achieve efficient production of target products through the artificial design and modification of biological systems. This field possesses revolutionary innovative potential and can trigger transformations in science, technology, and industry. Over the past three decades, microbial engineering and synthetic biology have undergone profound interdisciplinary integration, greatly promoting the advancement of biotechnology and the upgrading of the bio-industry. These disciplines can optimize existing biochemical reactions and metabolic pathways, introduce exogenous metabolic pathways, and even create metabolic pathways that do not exist in nature, thus breaking through the limitations of natural organisms' synthetic functions and scope.

By systematically designing and transforming biological routes for product manufacturing to gradually replace chemical routes, microbial engineering and synthetic biology can address pain points in traditional methods and processes, such as high costs, difficulties in mass production, and large carbon emissions. These disciplines offer advantages in terms of being green, efficient, and low in energy consumption. This enables synthetic biology methods to break the inherent pattern of "the strong remain strong" established by large enterprises, providing latecomer companies with opportunities for surpassing growth, and thus serving as a disruptive presence in the industry. Currently, these methods have been widely applied in various fields, including biomedicine, materials and chemicals, agriculture, food, energy, and environmental protection.

2.6.2 Critical Scientific and Technical Issues:

(1) How to deeply analyze the biosynthetic gene clusters of high-value natural products, explore the biosynthetic mechanisms of key metabolic molecules and active natural products, and clearly characterize biosynthetic elements?

(2) How to systematically analyze and establish the metabolic and regulatory networks of production strains, conduct rational design and prediction, and discover common high-yield mechanisms?

(3) In the industrial fermentation process, how to analyze the dynamic changes in cell metabolism of industrial strains to identify new targets for strain modification and process optimization control points, thus accelerating their mass production progress?

(4) What substitution roles can microbial engineering products play in the traditional chemical industry? How to promote the high-value derivative applications of bio-based products and realize the formation of a bio-manufacturing industry chain?

2.6.3 Research Foundations and Conditions in China and Internationally

Microbial platforms based on synthetic biology modifications can achieve the production of high value-added compounds such as energy, chemicals, and pharmaceuticals from renewable raw materials. Once microbial engineering products break through the limitations of "mass producibility" and achieve industrialized production, they often exhibit competitive advantages or even fundamental substitution over traditional synthetic processes, leading to disruptive changes in the entire industry. American synthetic biologists have achieved efficient synthesis of artemisinic acid in Saccharomyces cerevisiae, which serves as the basis for completing the chemical semi-synthesis of the antimalarial drug artemisinin, representing an important application paradigm of synthetic biology. Chinese scientists have utilized high-yield farnesene in yeast to realize the chemical synthesis of isophytol, ultimately completing the chemical semi-synthesis of vitamin E and successfully breaking foreign monopolies. In addition, Chinese companies have also completed the bio-fermentation processes for long-chain diacids and L-alanine, both of which have completely replaced previous traditional production methods and successfully captured half of the global market share.

However, currently, many high-value active compounds are still only at the stage of achieving high yields and cannot realize absolute advantages over traditional processes in terms of productivity. Moreover, restrictions from relevant domestic laws and regulations have led to delays in industrialization. Examples include various plant-derived natural products produced using microbial engineering, such as lycopene, ginsenosides, and norcantharidin, which urgently require subsequent research investment and corresponding policy support.

To achieve "mass producibility" and "synthesizability" of high-value active compounds, in addition to traditional personalized modification strategies such as enzyme engineering, regulation of global metabolic networks, and optimization of fermentation and extraction processes, Chinese scientists have also gradually developed some general methods to increase yield and accelerate progress. For instance, the multi-enzyme self-assembly strategy is used to solve problems such as low efficiency and metabolic flow imbalance in artificially constructed synthetic systems. The high-efficiency precursor supply platform based on "directed synthesis metabolism" is utilized to achieve high-throughput mining of specific enzymes, functional enzyme libraries, and gene clusters, completing a comprehensive exploration from point to surface. The strategy of inverse biosynthetic prediction is employed to explore and discover new pathways for heterologous biosynthesis, breaking through the bottlenecks of natural pathways.

2.7 Metabolism and Biomaterials

2.7.1 Strategic Value

Biomaterials are a new type of high-tech material with specific morphology that directly influence the process of diagnosis or treatment through interactions with living organisms. The application of biomaterials in clinical settings has driven the development and innovation of contemporary medical technology. When interacting with human tissues, body fluids, and blood, biomaterials should possess good biocompatibility and biosafety, and can be manufactured into medical products that maintain vital functions, repair, replace, or compensate for the functions of human organs. The discovery and development of biomaterials have saved countless lives and improved the quality of life. Moreover, with the development of the materials industry and the widespread application of artificial organs, the creation of new biomaterials has become an important component of the new technological revolution. Researching the metabolic mechanisms of biomaterials in biological systems and developing biomaterials without adverse reactions such as toxicity, sensitization, irritation, genetic toxicity, and carcinogenicity to the human body have significant scientific and practical significance.

2.7.2 Critical Scientific and Technical Issues:

(1) How to utilize metabolic biology research methods to deeply understand the

interaction mechanisms between biomaterials and living organisms, and discover the key metabolic pathways and metabolites through which biomaterials influence living organisms?

(2) How to leverage the interaction mechanisms and key metabolic pathways between biomaterials and living organisms to optimize the design and synthesis of biomaterials in depth, thereby achieving the biologicalization of various biomaterial functions?

(3) How to combine interdisciplinary methods from biology, materials science, engineering, and artificial intelligence to simulate the interactions between various materials and biological systems at the metabolic level, thus elucidating the biological mechanisms for realizing biomaterials with specific functions?

(4) How to utilize the metabolic characteristics of biomaterials with specific functions to explore biomaterials with application potential through high-throughput screening of biomaterials with corresponding functions?

(5) How to establish early detection and warning methods for metabolic diseases by combining research on biomaterials and disease biomarkers?

2.7.3 Research Foundations and Conditions in China and Internationally

Since the 1970s, the country has provided continuous and strong support for basic research on biomaterials through policies and scientific research investments. Relevant research capabilities have significantly improved, and the bio-industry has taken initial shape. According to statistics, from 2015 to 2022, over 210,000 academic papers were published in the field of biomaterials. Among them, Chinese scholars published a total of approximately 70,000 papers, accounting for about 32% and ranking first globally. At the same time, China has established a comprehensive and independent industrial system, becoming a major manufacturing country in the world. Under equivalent international technological conditions, "Made in China" has low costs, high cost-effectiveness, and huge market competition space. China possesses the research and development foundation, industrial foundation, and market space needed for the accelerated development of the biomaterials industry. In 2020 and 2021, the market size of China's biomedical materials industry reached 400 billion yuan and 480 billion yuan, respectively. However, it must be pointed out that currently, most domestic biomedical materials research and development still remain at the basic research stage, and a large portion of the domestic biomaterials market is still occupied by foreign products. Especially in the field of high-end biomaterial products, foreign products even occupy over 90% of the market share. Although some startups are engaged in the early research and development of biomaterials, most of them rely on the introduction of foreign intellectual property rights and lack independent self-control. Therefore, conducting metabolic characteristic research on China's independently developed biomaterials and combining them with biomedical needs can build a bridge between basic research and industrial manufacturing of biomaterials in China.

2.8 Metabolism and Biomass Energy

2.8.1 Strategic Value

Energy constitutes the foundation and driving force for social development, closely intertwined with national security and social stability. The current energy structure, predicated on petrochemical resources, exhibits evident unsustainability in its development trajectory. Renewable energy, defined as energy sources in nature that remain undiminished by human utilization and possess regenerative capacity, is characterized by its clean and low-carbon attributes, representing a pivotal direction for the advancement of energy technologies. Bioenergy, derived from biomass, is a significant form of renewable energy, with biomass being the sole renewable carbon resource on Earth.

The process of bioenergy development and utilization encompasses the production, collection, processing, and conversion of biomass. Initially, solar energy is transformed into chemical energy through photosynthesis in plants, stored within biomass. Biomass can release chemical energy through combustion to provide heat or generate electricity. It can also undergo carbon chain restructuring via chemical catalysis to produce bio-based fuels such as aviation fuel and diesel. Furthermore, following pretreatment, biomass can be subjected to biological fermentation and conversion to manufacture high energy density substances/fuels, including alcohols, terpenes, hydrocarbons, and lipids. Fundamentally, bioenergy technology harnesses biological platforms (plants, microorganisms) to compress solar energy across temporal and spatial scales, converting it into high energy density fuels, electricity, and heat. At the material level, this process is accompanied by the transformation of low-energy carbon dioxide molecules into high-energy multi-carbon molecules, driven by metabolic activities at the reaction, pathway, cellular, individual, and population levels. The development of bioenergy technologies necessitates systematic support from metabolic biology and technology across multiple links and dimensions.

2.8.2 Critical Scientific and Technical Issues

(1) How can the complex structure and regulatory hierarchy of lignocellulosic biomass be investigated to elucidate the key constraining mechanisms influencing the efficiency of lignocellulosic biodegradation, and explore the adaptability between biomass and enzymes, microorganisms, and microbial communities?

(2) How can the barriers to gene delivery and editing in energy plants be overcome to cultivate high-yielding, fast-growing, stress-resistant, and easily processable energy plants through cell wall engineering and multi-trait aggregation, and establish "ecological energy farms" to utilize marginal lands for producing high-quality biomass resources?

(3) Considering the structure and composition of plant biomass, how can the affinity, recognition, and cleavage patterns of enzymes and microorganisms towards biomass macromolecules and complexes be deciphered, and highly efficient cellulase systems and microorganisms/microbial communities be developed to achieve low-cost, high-efficiency conversion of biomass to fermentable sugars?

(4) How can the response and adaptation mechanisms of microbial cells and biofuel cell factories to diverse stress factors be elucidated, and advanced biofuel synthesis routes with high atomic economy be developed to enhance the ability and efficiency of biofuel cell factories in utilizing and converting biomass sugars?

2.8.3 Research Foundation and Conditions in China and Internationally

Through decades of practice, bioenergy technologies and industries, represented by fuel ethanol, have made significant progress. In particular, first-generation biofuel technologies, utilizing food crops such as corn or high-sugar crops like sugarcane as raw materials, have secured a crucial position in the energy supply structure of some countries. For instance, the ethanol content in gasoline exceeds 20% in Brazil and 10% in the United States. China has also cumulatively blended and used over 300 million tons of fuel ethanol. With the support of a series of policies, it is expected to play a more vital supporting role in the national energy structure.

However, biofuel technologies based on food/high-sugar crops inherently have the drawback of "competing with humans for food and with food for land," facing severe limitations in their development potential against the backdrop of an intensifying global food crisis. Therefore, it is imperative to develop new bioenergy manufacturing technologies using non-food biomass and energy plant biomass as raw materials. Consequently, the main directions of international bioenergy technology research and development include: replacing food crops with non-food energy crops on the supply side, utilizing marginal lands such as saline-alkali lands and tidal flats instead of arable land for energy biomass production, and replacing complex, high-cost pretreatment processes with one-step, low-cost biomass degradation and saccharification technologies on the production side, thereby achieving efficient synthesis of diversified biofuel products. In this process, the development of technologies such as "creation of high-quality energy biomass resources," "efficient biomass deconstruction and separation," and "efficient biomass conversion and targeted biofuel synthesis" will play a crucial role, which cannot be achieved without major scientific discoveries and theoretical breakthroughs in the field of biological cell matter-energy metabolism mechanism research.

2.9 Metabolism and Carbon Neutrality & Peak Carbon Emissions

2.9.1 Strategic Value

Carbon peaking refers to the maximum level of carbon dioxide emissions reached in a specific year, followed by a decline. Carbon neutrality, on the other hand, implies that within a certain period, the carbon dioxide produced by the activities of a specific organization or the entire society is absorbed and offset through natural and artificial means such as afforestation, ocean absorption, and engineering sequestration, achieving relative "zero emissions" of carbon dioxide from human activities. Increasing carbon dioxide sequestration and reducing carbon dioxide emissions are essential for achieving carbon neutrality and peak carbon emissions. Promoting carbon sequestration through nitrogen enhancement, improving plant photosynthetic capacity, and synthetic biology-based carbon fixation are important approaches to balance carbon dioxide.

A crucial component of the "Dual Carbon" target plan is to continuously consolidate and enhance the carbon sink capacity of ecosystems. In China, forests, farmlands, and shrublands, the three largest carbon sink sources, sequestered an amount of carbon equivalent to 14.1% of fossil fuel carbon emissions during 2001-2010. Applying the concepts and design capabilities of metabolic biology to carbon dioxide conversion and utilization is an innovative solution for achieving China's "Dual Carbon" goals. Biological pathways from carbon dioxide to fuels, materials, and chemicals can be constructed, creating new industrial routes for efficient synthesis of drugs, food, and other products, thereby establishing a clean, green, and sustainable new material supply model.

2.9.2 Critical Scientific and Technical Issues:

(1) How to develop multi-scale, high-efficiency photosynthetic system design models to explore and design key high-efficiency photosynthetic genes, and integrate

high-efficiency photoreaction and carbon metabolism characteristics, protein structural biology foundations, and molecular genetic regulation strategies?

(2) Based on nitrogen-promoted plant carbon sequestration efficiency, how to explore and design key components to regulate plant photosynthetic carbon fixation through symbiotic nitrogen fixation mechanisms, and efficiently create carbon-sequestering plant root systems?

(3) When designing artificial carbon fixation biological systems, key issues include how to design and reconstruct carbon fixation metabolic and regulatory networks, assemble and adapt artificial carbon fixation components and functional modules, and construct efficient and practical artificial carbon fixation systems.

2.9.3 Research Foundations and Conditions in China and Internationally

The key to improving plant carbon sink capacity is to enhance plant photosynthetic efficiency. In 2013, the Bill & Melinda Gates Foundation, the U.S. Foundation for Food and Agriculture Research, and the UK Department for International Development jointly established the Realizing Increased Photosynthetic Efficiency (RIPE) project. At the same time, the Gates Foundation also launched the C4 Rice Project, aiming to research technologies for transforming C3 crops into C4 photosynthetic crops. With RIPE and the C4 Rice Project as pivotal points, multiple international photosynthesis synthetic biology research hubs have been established, forming highly collaborative international research teams and creating key tools, biological resources, and research platforms for conducting photosynthesis synthetic biology research, leading to a series of important advances in plant photosynthesis biology. Meanwhile, the Salk Institute in the United States has established a project to combine photosynthetic efficiency improvement with root system remodeling, modifying root system components, creating deep root systems, increasing plant carbon fixation, and prolonging the residence time of fixed carbon in the soil, thereby enhancing plant carbon sink capacity.

China's development in different areas of photosynthesis improvement is highly uneven. In the field of photosynthesis systems biology, China's research is in a leading position internationally. In the field of photosynthesis molecular engineering, China has conducted systematic research in areas such as photorespiration bypass creation, photoinhibition, and genetic control of natural variation in photosynthetic efficiency. In terms of nitrogen-promoted carbon fixation, China has made important contributions in nitrogen nutrient absorption and symbiotic nitrogen fixation. However, in the field of photoprotection mechanisms and their application potential, China's research lags behind international levels. In terms of root system component remodeling, both international and domestic research is in the initial stages.

Although Chinese scientists have made important progress in recent years in the artificial biological conversion of carbon dioxide and other one-carbon resources, the design and construction of carbon fixation pathways, and their applications, there are still gaps compared to international advanced levels in terms of basic theories, enabling technologies, core systems, and industrial technology advancements. Therefore, strengthening the application of synthetic biology in carbon neutrality and energy conversion is a major scientific and technological task currently facing China.

2.10 New Technology Development and Metabolomics

2.10.1 Strategic Value

Changes in metabolites can directly reflect the physiological and pathological states of living organisms, serving as a bridge connecting genes and biological phenotypes. Metabolomics primarily focuses on studying the content, distribution, and dynamic changes of small-molecule metabolites within living organisms. It is one of the essential technical means to investigate metabolic homeostasis, disorders, and regulatory mechanisms at the omics level. Metabolomics is an interdisciplinary field closely related to various disciplines such as biological sciences, analytical chemistry, chemometrics, microbiology, synthetic biology, and bioinformatics. Integrating metabolomics data with omics data at different levels, such as genomics, transcriptomics, proteomics, phenomics, and microbiomics, can provide mutual validation and complementation, contributing to a more comprehensive understanding of life processes and disease development mechanisms, and promoting basic biological research and numerous scientific studies related to human health and diseases.

The development of metabolomics research is inseparable from the advancement of various new technologies and methods. Currently, no single technology can simultaneously detect all metabolites in biological samples. Therefore, metabolomics research is still in a period of rapid development, with many technical issues that urgently need to be addressed. It is imperative to develop new technologies and methods based on nuclear magnetic resonance and mass spectrometry for precise qualitative and quantitative analysis of metabolites.

2.10.2 Critical Scientific and Technical Issues:

(1) How to develop analytical methods suitable for highly complex biological systems to achieve large-scale, high-efficiency analysis of small-molecule metabolites (including known and unknown metabolites) within living organisms?

(2) How to track metabolic reaction pathways of metabolites in living organisms on a large scale at different scales (single cells and organelles) and dimensions (time and space) to determine their spatiotemporal dynamic changes?

(3) How to efficiently discover functional metabolites and directly and accurately study their regulatory mechanisms in physiology and pathology?

(4) How to utilize functional metabolites for early prevention, diagnosis, and treatment of diseases to promote the development of metabolomics research?

2.10.3 Research Foundations and Conditions in China and Internationally

Nuclear Magnetic Resonance (NMR) technology has irreplaceable advantages in non-destructive testing, high-throughput analysis of biological samples, and in situ detection of tissue samples. NMR spectrometers are mainly monopolized by foreign companies such as Bruker, but the gradual rise of domestic spectrometers provides strong support for scientific and technological innovation in China. High-field NMR spectrometers developed by the Innovation Academy for Precision Measurement Science and Technology of the Chinese Academy of Sciences have been industrialized. Since the 1990s, research and development of a new generation of NMR instruments, such as Dynamic Nuclear Polarization (DNP) instruments, have been carried out. DNP technology can increase the detection sensitivity of NMR by 3-5 orders of magnitude, which is an innovative technology urgently needed in cutting-edge fields such as metabolite imaging. Currently, the team led by Academician Liu Maili has completed the development of an engineering prototype for liquid DNP, successfully achieving the detection of various heteronuclei, providing important technical support for the development of metabolic biology and related technologies in China. The independently developed lung hyperpolarized gas Magnetic Resonance Imaging (MRI) equipment by the team led by Zhou Xin has, for the first time internationally, realized the quantitative and visualized assessment of pulmonary microstructure, ventilation, and gas exchange function in discharged COVID-19 patients, providing new opportunities for breakthroughs in related fields.

The major manufacturers of mass spectrometers required for metabolomics research are foreign companies, including Thermo Fisher Scientific, Agilent, and AB Sciex from the United States, Bruker from Germany, and Shimadzu from Japan. Currently, only triple quadrupole mass spectrometers can be domestically substituted, but their performance still lags behind foreign cutting-edge products by about 10-20 years. In the field of high-resolution mass spectrometry (such as Orbitrap and ion mobility mass spectrometry), there is a lack of corresponding domestic substitutes, and related basic research is relatively limited. Tsinghua University, Ningbo University, Northwest Institute of Nuclear Technology, and Dalian Institute of Chemical Physics of the Chinese Academy of Sciences are currently conducting a small amount of cutting-edge research. Hexin

Instruments has achieved mass production of its independently developed rapid liquid chromatography-tandem quadrupole time-of-flight mass spectrometry products in 2023, but their stability still needs to be proven over time.

In terms of data analysis, the analysis of raw mass spectrometry data and large-scale qualitative analysis of metabolites in metabolomics currently rely mainly on foreign software and databases. Domestic researchers can only access limited use by logging into foreign websites. In the past decade, domestic researchers have been conducting independent research and development. For example, the teams led by Xu Guowang and Zhu Zhengjiang from the Chinese Academy of Sciences are developing metabolomics data analysis software and databases with independent intellectual property rights (such as MetDNA and Met4DX).

In the past decade, China has gradually increased support and investment in metabolomics research by purchasing advanced mass spectrometry instruments and introducing several core researchers in the field of metabolomics to return to China and establish relevant platforms, greatly promoting the technological development in this field in China. Several research teams have gained certain international influence and have made important progress.

Chapter 3 Development Strategies and Policy Recommendations in Metabolic Biology in China

The interdisciplinary integration of metabolomics with multiple other disciplines has profoundly impacted vital areas of the national economy, including public health, food security, emerging industry development, and ecological and environmental protection. Over the past decade, thanks to the long-term and stable support from the government in terms of policies and scientific research, China's research capabilities in metabolomics have significantly improved, and the bio-industry has taken initial shape.

However, there are still some pressing issues and challenges in the field of metabolomics in China. First, there are relatively few original innovative achievements, and the market share of high-end products is low. Second, research resources are scattered and lack effective integration. Moreover, key detection instruments and databases are heavily dependent on foreign countries, posing the risk of being "choked off."

In order to further advance the development of metabolic biology in our country and enhance its contribution to the national economy, it is recommended that the state formulate and implement key projects in metabolic biology and establish a National Metabolic Biology Science and Technology Center. By strategically planning and integrating resources at the national level, clear research directions and priorities can be established, directing basic research towards critical scientific issues related to national health and economic growth. Concurrently, collaboration between industry, academia, and research institutions is encouraged to actively explore the application of metabolic biology in relevant industries. There is also an emphasis on the creation of a comprehensive instrument product chain and the development of a proprietary database, which will provide substantial support for the advancement of artificial intelligence and precision medicine.

3.1 Establish Key Special Projects in Metabolic Biology

By concentrating financial support, we advocate for a multidimensional strategy that encompasses independent exploration, top-level planning, and market demand orientation. This approach aims to achieve proactive advancements in addressing major scientific issues and breakthroughs in key technologies within metabolic biology. It will facilitate seamless integration from basic scientific research to industrial application, thereby accelerating innovation and the translation of technological achievements in the field of metabolic biology. Moreover, this initiative is expected to promote the healthy and sustainable development of related industries.

(1) Establish multi-dimensional research platforms to advance precise prevention and treatment of metabolic diseases

High-throughput research platforms need to be established, including utilizing individualized cell models and organoid systems, combined with multi-omics technologies and drug screening platforms, to systematically study pathogenic genetic variations and key gene regulatory networks. Develop new technologies to investigate metabolic heterogeneity of tissue microenvironment cells and explore new strategies for targeting specific cells to improve metabolic diseases. At the same time, develop in vivo imaging techniques to map metabolic profiles, promote the application of primate animal models in disease research, and ultimately establish a precise disease prevention and treatment system based on Chinese population data.

(2) Deepen the integration of basic research and clinical research to open up new avenues for diagnosis and treatment of metabolic diseases

Comprehensively utilize clinical cohorts, animal models of diseases, multi-omics research methods, as well as molecular biology and chemical biology approaches to strengthen basic research combined with clinical practice. Establish multi-level and multi-dimensional integrated activity screening systems and research models that better simulate human metabolic processes. Develop metabolic disease biomarkers and focus on the genetic characteristics of different populations and individuals to carry out precision medicine and drug development, providing innovative treatment and intervention solutions for metabolic disorder-related diseases.

(3) Construct a new model of integrated "metabolism-proactive health" management

Establish an integrated "metabolism-proactive health" intervention platform. Through interdisciplinary cooperation, conduct in-depth research on the key elements of metabolism and health and their interactions, develop precision intervention programs and personalized health guidance, and promote innovation and practice in metabolic health management. Provide comprehensive, efficient, and personalized metabolic health management services to the public, improving public health levels and quality of life.

(4) Multidimensional Exploration of Microbial Metabolic Networks, Opening a New Chapter in Disease Prevention and Control

Through interdisciplinary research, the role of disease-related microorganisms and their metabolites shall be elucidated. Key technological platforms shall be established, and artificial intelligence systems shall be utilized to analyze microbial metabolic networks, revealing the dynamic changes of microorganisms and their metabolites during disease processes. The intersecting networks of microbial and host metabolism shall be deciphered, leading to the discovery of new disease- and health-related microorganisms and crucial genes, thus providing novel targets and strategies for the prevention and control of major diseases.

(5) Promoting Plant Metabolomics Research and Industrial Development

It is recommended to prioritize support for research directions such as biosynthesis, regulation, physiological functions, and mechanisms of plant metabolites; metabolic reprogramming mechanisms in plant development and stress responses; and natural variation and evolutionary patterns of plant metabolic diversity. Efforts shall be made to strengthen the construction of national-level R&D platforms and infrastructure, guide enterprises to establish relevant funds, and create a favorable environment in terms of software and hardware. Collaboration among universities, research institutes, and enterprises shall be promoted to form an R&D innovation chain for industrialization and to establish relevant standards, identification and labeling systems, as well as market entry and exit mechanisms.

(6) Planning the Coordinated Development of Biomaterials, Bioenergy, and Biological Carbon Sequestration in Basic Research and Industry

High-efficiency photosynthetic element libraries and phenotypic screening platforms shall be constructed, and a national R&D center for biological conversion of one-carbon gases shall be established. The application of metabolomics in bioenergy production shall be strengthened, customized biomaterials shall be developed, and progress in biomaterials for precision medicine and other fields shall be promoted. Original and leading biomaterial research shall be intensified, and the commercialization and industrialization of basic research results shall be supported.

(7) Independent Innovation: Advancing the Development of Next-Generation Metabolomics Technologies

The development of nuclear magnetic resonance and mass spectrometry instruments with independent intellectual property rights shall be accelerated, and breakthroughs in key core technologies shall be achieved to realize domestic substitution. Simultaneously, next-generation metabolomics technologies shall be planned, including spatial metabolomics, single-cell/subcellular organelle metabolomics, unknown metabolite structure identification, tracing of multiple metabolic pathways in live cells or animals, and proteomic detection of novel protein modifications. These advancements shall facilitate high-precision, high-coverage, and real-time quantitative analysis of metabolites, providing crucial scientific evidence for future drug development and treatment strategies.

3.2 Establishment of National Metabolic Biology Science and Technology Center

The National Metabolic Biology Science and Technology Center shall integrate research strengths from both domestic and international realms in the field of metabolic biology, providing cutting-edge instruments, database resources, and analytical tools to furnish researchers with the necessary support to propel the progression of metabolic biology research. Furthermore, metabolic biology is an interdisciplinary field that intersects biology, chemistry, medicine, and other domains; the center shall facilitate the establishment of collaborative platforms across different disciplines, fostering interdisciplinary integration and engendering novel research directions and breakthroughs. Additionally, the center shall create uniform experimental platforms and data standards, mitigating redundant construction and resource wastage, enhancing research efficiency, and accelerating the research process through shared data and experiences, thus avoiding futile explorations. Moreover, metabolic dysregulation constitutes a significant pathological basis for many major diseases. The center shall undertake fundamental research and translational applications specific to metabolic diseases, offering new strategies and methods for disease prevention, diagnosis, and treatment. Ultimately, the center shall attract and cultivate outstanding talent within the field of metabolic biology, providing a conducive scientific environment and development platform to encourage the emergence of young talent, thereby reserving high-level scientific and technological personnel for the nation.

(1) Concentrate efforts at the national level to establish a metabolic instrumentation analysis platform.

Establish a National Metabolic Instrumentation Analysis Center, equipped with internationally advanced large-scale instruments such as mass spectrometry and nuclear magnetic resonance, to offer high-throughput, high-quality analytical testing services. Create a reporting system based on metabolic characteristics, achieving dynamic real-time monitoring of high-throughput metabolism and constructing a drug screening platform. Conduct joint research initiatives, strengthen talent team building, promote international exchange and cooperation, and break through core technology bottlenecks in metabolite detection and data interpretation, thereby enhancing China's original research capability in metabolism. Ultimately form a platform system that is rational in layout, resource-sharing, technologically advanced, and service-efficient, to powerfully support the advancement of China's metabolic research and related industrial development.

(2) Build a national-level metabolic disease resource repository.

Benchmarking against internationally advanced biomedical resource banks, such as the UK BioBank, create a metabolic disease causative gene, treatment, and prevention information resource repository with Chinese independent intellectual property rights, and provide a convenient and efficient data retrieval, analysis, and sharing platform. Provide significant research tools and data support for Chinese researchers to accelerate the elucidation of the pathogenesis of metabolic diseases, the development of new drugs, and the realization of precision medicine. Concurrently, the construction of this resource repository will also help promote interdisciplinary integration, propelling the application of emerging technologies such as bioinformatics and artificial intelligence in research on metabolic diseases. It will also enhance China's international discourse and influence in this field, and strengthen exchanges and cooperation with international counterparts.

(3) Establish a novel natural product structural library with Chinese characteristics.

Systematically collect and organize resources such as animals, plants, and microorganisms unique to China, establish a database of natural metabolic product sources, and provide a foundation for the discovery of novel compounds. Innovate separation and purification technologies, establish structural analysis platforms, conduct systematic biological activity evaluations, strengthen industry-academia-research cooperation, and improve intellectual property protection. Through these measures, establish a structural library of natural metabolic products with independent intellectual property rights, novel structures, and defined functions, providing support for research and industrial applications of natural metabolic products, and promoting the sustainable use of China's natural metabolic product resources and the development of the biomedical industry.

(4) Develop artificial intelligence systems to analyze metabolic networks and discover population and individual metabolic characteristics.

Integrate machine learning algorithms, deep learning models, network analysis methods, multi-omics data integration, knowledge graph mining, causal inference models, and translational medicine applications, etc., to comprehensively utilize these methods to analyze the metabolic networks and characteristics of populations and individuals from multiple dimensions and levels, providing new ideas and tools for metabolomics research and precision medicine applications. Change the current situation where China's basic research in this field heavily relies on foreign advancements.

Develop virtual cell and digital models, integrating disciplines such as life sciences, mathematics, and computational science, to establish modular models and create comprehensive models, and carry out the algorithm and software development needed for various applications based on virtual cells and digital biology.