Establishment of Scientific Evidence for Kampo Formulations

Aiming to Clarify the Mechanism of Efficacy

A large number of pharmaceutical products have been made by identifying an active ingredient derived from a natural substance and synthesizing it. However, only a fraction of the countless active ingredients in crude drugs have been identified. Moreover, in Kampo medicines, there are actually diverse and complex effects, such as effects produced by a single ingredient, effects produced by the combination of multiple ingredients, and effects produced by ingredients when metabolized inside the body after administration. This is why there is endless potential for research investigating mechanisms of efficacy for Kampo medicines.

At Tsumura, we have focused resources on drug-fostering research*1 since fiscal 2004, working to clarify why something is effective and what is having the effect while building evidence related to efficacy and safety. The huge volume of data that we have accumulated, including internal material that has not been published, is one of the Company's assets. Since fiscal 2016, we have established our priority research themes as geriatric health, cancer (supportive care), and women's health. These are social issues with prominently expanding markets. We are promoting efforts to build evidence for Kampo medicines in these areas.

Kampo Medicine Research Is Science

Recently, our research has also focused on searching for responder markers*2 aiming to provide scientific clarification of patterns in Kampo medicine. We are also focusing on research into areas such as genes, proteins and biometabolites, and intestinal flora, along with research using clinical databases, in order to shed light on the complex mechanisms of action of Kampo medicines, as well as individual differences in effect.

For Tsumura, research into Kampo medicines goes beyond the category of chemicals, which looks at the nature of substances and changes in phenomena, to include the in-depth pursuit of systematic science backed by theory. We will continue to engage in even deeper research into Kampo medicines derived from natural substances, enhancing our experience in clinical settings while publicizing knowledge about their efficacy and safety through scientific evidence.

*1 Research activities for accumulating basic and clinical data to establish evidence for diseases that have been resistant to new Western drugs and for which prescription Kampo formulations have demonstrated special efficacy
*2 Physiological indexes to differentiate patients who have high potential to show effects in response to treatment (responders)

Research Flow for Drug-Fostering Program and "Growing" Formulations

Selection of areas and diseases	We select certain diseases in areas within the existing scope of approval and with high medical needs, for which new Western drugs have not been successful and where prescription Kampo formulations have demonstrated special efficacy.
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Basic research	Through multiple basic research projects, we clarify mechanisms of action and confirm the main active ingredients, announcing our findings in academic papers and at conferences.
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Clinical research (efficacy)	Through discussions with key opinion leaders (KOLs) and appropriate clinical research, we confirm the efficacy of Kampo medicines in clinical testing and announce our findings in academic papers and at conferences.
Clinical research (safety)	Through clinical pharmacokinetics testing, we confirm the pharmacokinetics of each ingredient in people and announce our findings in academic papers and at conferences. In addition, we also conduct surveys on the frequency of side effects with the objective of proactively gathering side effect information.
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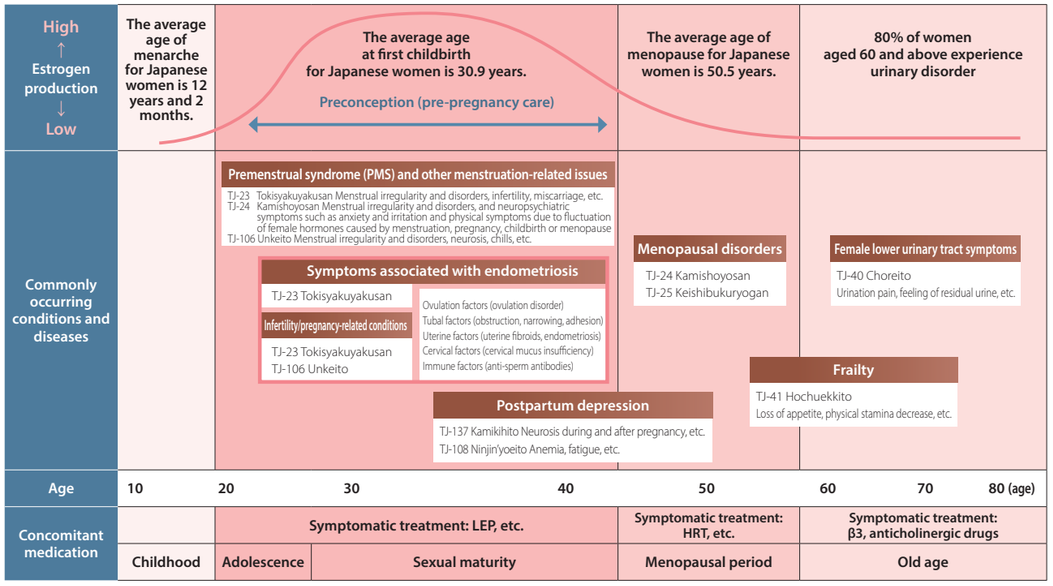
Information provision activities	We provide information to medical professionals and medical societies, among others, and promote the appropriate use of Kampo medicines.
Increase in write-ups and level of recommendation in treatment guidelines	We aim to expand the areas where Kampo medicines are prescribed as a standard treatment through write-ups in treatment guidelines.
↓	
Responder research using KAMPOmics®	We conduct responder research to narrow down formulations even further and clarify the patterns scientifically, announcing our findings in academic papers and at conferences. Moreover, from research and development on individually tailored treatments, we aim to establish optimal Kampo treatments for each patient (personalized medicine).

Concentrating Research Resources in Important Domains

In addition to its strategic drug-fostering program formulations and "growing" formulations, Tsumura has been striving to obtain write-ups in treatment guidelines in three important domains, which it set out in fiscal 2016. The first domain is geriatric health, where we are conducting joint research with national research institutes and others on the themes of frailty, dementia, and cardiovascular disease. We aim to extend healthy lifespans with Kampo formulations. The second domain is cancer (supportive care), where we are advancing research into inflammation in the body and the immune system, including countermeasures for side effects from chemotherapy drugs. We aim to improve the physical condition of patients and help to support them at work. The third domain is women's health, where we are constructing a platform for standard Kampo treatments by clearly setting out research strategies for each life stage to contribute to active lives for women.

Research Strategy for Each Life Stage in the Women's Health Domain



Promotion of CMC Research

CMC*3 is an essential series of processes for pharmaceutical manufacturing and quality control. Tsumura has established the CMC Development Research Laboratories at its Ibaraki research site to conduct R&D on manufacturing technologies that can be applied to the inherent quality characteristics of Kampo formulations and to develop multi-component analysis technologies and quality control technologies to ensure continued stable production. Other responsibilities of the laboratories include manufacturing and quality assurance of investigational new drugs and setting rational quality standards based on the Japanese Pharmacopoeia, while also making reference to laws and regulations in other countries.

CMC research will play an important role in enabling Kampo medicines to contribute to the health and treatment of patients around the world going forward by building quality evidence for international standards. The reason for this is that in the United States and Europe, where synthetic medicines (Western medicines) are mainly used, CMC research provides efficacy and safety evidence to regulatory authorities to prove the quality of Kampo medicines, which have complex combinations of ingredients. We also need to obtain approval for our unique, rational manufacturing control and quality control systems.

Furthermore, our challenge of building an even more advanced GMP*4 system than now, and obtaining approval for it from regulatory authorities, is without precedent anywhere in the entire industry. With a full understanding of the thinking behind synthetic medicines, we are making steady progress in R&D aimed at scientifically elucidating the quality characteristics of Kampo medicines in order to obtain regulatory approval.

*3 Chemistry, Manufacturing, and Control
*4 Good Manufacturing Practice: A standard for pharmaceutical manufacturing control and quality control

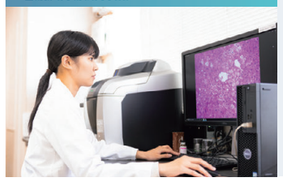
Accumulating In-House Technologies

Tsumura's three research and development laboratories are accumulating proprietary technologies and expertise related to their respective missions and research fields. The three research laboratories are striving to advance Kampo medicine research while developing closer coordination with each other.

Tsumura Kampo Research Laboratories

Tsumura Kampo Research Laboratories is engaged in both basic and clinical research aimed at advancing the standardization of Kampo treatment. In basic research, we focus on clarifying the mechanism of effect of Kampo medicines based on evidence from clinical research and on creating data to assist with personalized medicine. We are also accumulating expertise on the creation of experimental model animals and evaluation methods specialized for Kampo medicines. In clinical research, we are conducting in parallel evaluation of markers that have been used to evaluate Western medicines and evaluation specific to Kampo medicines. We are collecting evidence as we investigate the relationship between these. Through these research activities, we are striving to contribute to the standardization and spread of Kampo treatment.

Tsumura Advanced Technology Research Laboratories



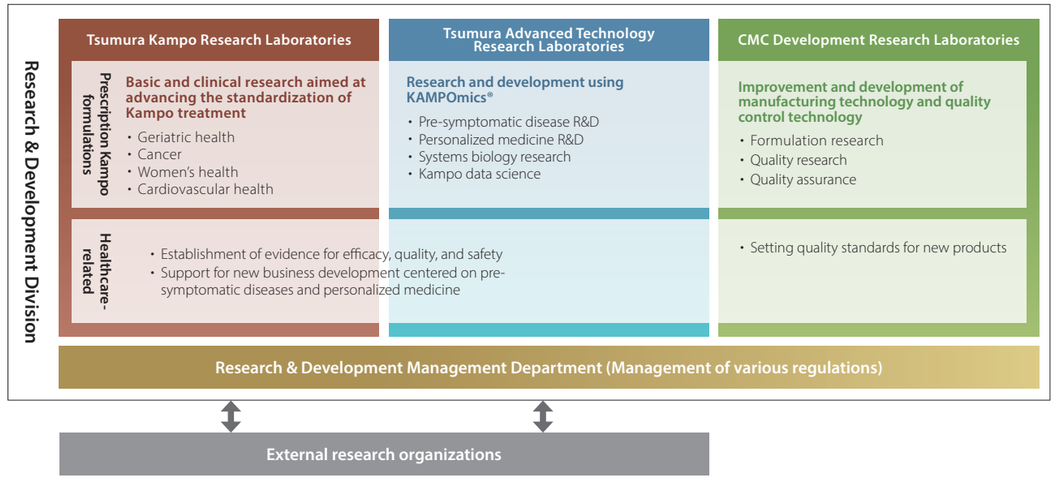
Tsumura Advanced Technology Research Laboratories is engaged in establishing and advancing mass spectrometry technology for clarifying the action of Kampo medicines on living organisms, gene analysis technology, intestinal flora analysis technology, and systems biology,*5 among others. The main characteristic of the facility is its construction of a platform unique to Tsumura that integrates and systematizes these proprietary technologies as KAMPOmics®. Using this platform, we will conduct research into the efficacy, quality, and safety of multi-component formulations, scientifically clarify pre-symptomatic diseases, and create biomarkers for use in personalized Kampo medicine. In parallel with this, we have also started building a Kampo diagnostic support system.

*5 A field of research that seeks to provide a comprehensive explanation of biological functions by focusing on the interaction between genes, proteins, metabolites and other biological factors

CMC Development Research Laboratories

CMC Development Research Laboratories is mainly responsible for improvement and development of manufacturing technology and quality control technology related to Kampo extract powder and formulations, and manufacturing and quality assurance of investigational new drugs. The laboratory has a number of patents related to new analysis technologies used in quality testing and quality control for exogenous impurities. In particular, for analysis methods related to agrochemical residue, it has patents not only in Japan, but also in the United States and China. In light of the Company's new businesses going forward, the laboratory is expected to acquire patents combining new plant and Kampo extract extraction methods, their compositions, and pharmacological actions, and to establish industrial-scale manufacturing technologies.

R&D Structure



Using KAMPOmics® to Promote the Scientific Study of Kampo

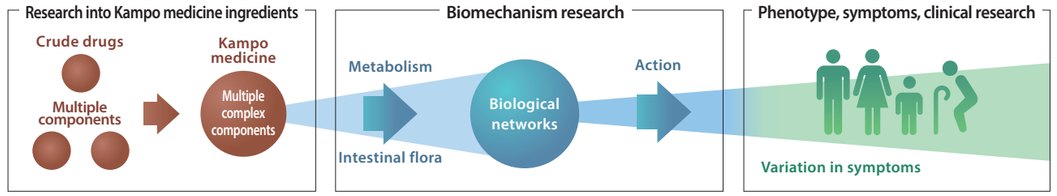
KAMPOmics® is a research package developed by Tsumura. It combines research on cutting-edge technological fields where Tsumura has strengths (metabolomics,*6 genetics, intestinal flora, systems biology, etc.), and is formulated to gain a comprehensive understanding of Japanese traditional Kampo medicine, and the action mechanisms of Kampo medicines with their multiple components and complexities. Looking ahead, we will leverage this research system to accelerate applied research towards our goals of establishing the most appropriate Kampo treatment for each patient (personalized medicine) and the scientific study of pre-symptomatic diseases.

In our initiatives for personalized medicine, we are promoting research that will help to clarify common characteristics of patients for whom Kampo medicines have shown a prominent effect, and the development of an AI Kampo diagnostic support system that will conduct science-backed diagnosis of patterns, which is considered to be in the realm of accomplished Kampo practitioners. Meanwhile, for the scientific study of pre-symptomatic diseases, we first created a scientific perspective on what constitutes a pre-symptomatic condition to enable us to understand, as a system, the status of the body from pre-symptomatic disease to disease, and we are now concentrating on research into biomarkers to objectively understand the effects of prescription Kampo formulations in relation to pre-symptomatic treatment, prevention of aggravation, and prevention of relapses.

We will develop the results obtained through this series of research activities from our proprietary intellectual property to development, aiming to rapidly achieve social implementation of the Company's technologies through initiatives such as developing a service that objectively evaluates individual physical conditions and symptoms, and building a pre-symptomatic disease diagnosis system.

*6 A field of research that performs comprehensive analysis of metabolites and Kampo medicine components within the body using a mass spectrometer and other means

Using KAMPOmics® Technologies



Multicomponent analysis of Kampo and crude drugs
We conduct comprehensive analysis of components included in Kampo medicines and crude drugs, and utilize this in searching for active ingredients in pharmacological research. We also examine the quality evaluation of Kampo formulations using a Kampo medicine multicomponent profile.

Systems biology
We conduct research that seeks to provide a comprehensive explanation of biological functions by focusing on the interaction between genes, proteins, metabolites and other biological factors.

Pharmacokinetics
We evaluate the pharmacokinetics and pharmacological interaction of the active ingredients in Kampo medicines.

Microbiome
We are clarifying the interaction between intestinal flora and Kampo medicines, and examining the possibility that intestinal bacteria could be a biomarker that stipulates the effects and side effects of Kampo medicines.

・Genome (gene sequence)
・Epigenome (modulation of gene expression)
・Transcriptome (transcripts/mRNA)
The involvement of genetic factors in the complaints for which Kampo medicines are effective, and the characteristics of gene expression related to pre-symptomatic diseases are becoming clear. Comprehensive genetic analysis is making progress on clarifying the pathophysiology of sensitivity to cold and the mechanism by which Kampo medicines are effective in treating it, including the identification of single nucleotide polymorphisms (SNPs) related to sensitivity to cold. Analysis of the transcriptome of senescence-accelerated mice identified intron retention (IR) as a pre-symptomatic condition related to aging, and we are examining the potential for IR to serve as a biomarker for pre-symptomatic diseases and the efficacy of Kampo medicines.

Proteome
We comprehensively measure the proteins in the body and clarify the impact of Kampo medicines on them to investigate their potential as biomarkers for pre-symptomatic diseases and the effects of Kampo medicines.

Metabolome (metabolites in the body)
We comprehensively measure low-molecule components (metabolites) such as amino acids and lipids in the body and clarify the impact of Kampo medicines on them to investigate their potential as biomarkers for pre-symptomatic diseases and the effects of Kampo medicines.

Data science
We are promoting the accumulation of evidence for Kampo medicine using medical big data.

Kampo diagnosis
We are working to develop an AI Kampo diagnostic support system.

・Pharmacology
・Clinical testing
In addition to pharmacological research, we also conduct systems biology research with various omics analyses, aiming to fully clarify the action of multi-component Kampo medicines to contribute to the scientific study of pre-symptomatic diseases and Kampo-based personalized medicine.