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Review Article

Strategic Outlook toward 2030: Japan's research for allergy and immunology – Secondary publication☆

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ABSTRACT

Strategic Outlook toward 2030: Japan's Research for Allergy and Immunology (*Strategy 2030*) is the national research strategy based on Japan's Basic Law on Measures Against Allergic Diseases, a first of its kind worldwide. This strategy was established by a multi-disciplinary committee consisting of administrators of the Ministry of Health, Labour and Welfare of Japan, young and senior experts from various research societies and associations, and representatives of patient and public groups. Whereas the issues of transition, integration, and international collaboration have yet to be solved in this research realm in Japan, identification of unmet needs, digitization of information and transparent procedures, and

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Japan
MHLW
Strategy

Abbreviations:
ABPM, Allergic Bronchopulmonary Mycosis; AERD, Aspirin-exacerbated Respiratory Disease; AI, Artificial Intelligence; AMED, Japan Agency for Medical Research and Development; CIRB, Central Institutional Review Board; DiHS, Drug-induced Hypersensitivity Syndrome; EMA, European Medicines Agency; FDA, Food and Drug Administration; HFSP, Human Frontier Science Program; IRUD, Initiative on Rare and Undiagnosed Diseases; J-RDMM, Japanese Rare Disease Models & Mechanisms Network; MEXT, Ministry of Education, Culture, Sports, Science and Technology, Japan; MHLW, Ministry of Health, Labour and Welfare, Japan; PMDA, Pharmaceuticals and Medical Devices Agency; PPI, Patient and Public Involvement; R&D, Research and development

strategic planning for complex problems (a process dubbed *MIERUKA* by the Toyota Way) are crucial to share and tackle the same vision and goals. The committee developed three specific actions focusing on preemptive treatment, interdisciplinarity and internationality, and life stage. The real success of *Strategy 2030* is made by the spontaneous contributions of doctors, dentists, veterinarians, and other medical professionals; basic and clinical research scientists, research supporters, and pharmaceutical/medical device companies; manufacturers of food, healthcare, and home appliances; and patients, their families, and the public. The hope is to establish a stable society in which people can live long, healthy lives, as free as possible from allergic and immunological diseases, at each individual life stage. This article is based on a Japanese review first reported in *Arerugi*, introduces the developmental process and details of *Strategy 2030*.

Introduction

Should Japan proceed with research on allergy and immunology, despite the increase in social security costs and the decrease in tax revenue following the progress of the super-aged society? If yes, from what perspective should the research be promoted? To address these questions, we planned and formulated *Strategic Outlook toward 2030: Japan's Research for Allergy and Immunology* (hereinafter, *Strategy 2030*) focusing on a process dubbed *MIERUKA*. It was originally a management technique used at Toyota to increase efficiency and effectiveness by making the steps more visible[1] and is now used in a broader sense. Herein, we defined *MIERUKA* as the identification of unmet needs, digitization of information, making the process transparent, and strategic planning for complex problems, toward safe societal development.

Japan has a long history of studying allergic and immunological diseases. Countermeasures instituted by the Japanese government were launched nearly half a century ago, and the national research project regarding childhood asthma treatment was first conducted in 1972.[2] Since then, the Ministry of Health, Labour and Welfare, Japan (MHLW) has played an essential role in tackling these major societal problems, and the Basic Law on Measures Against Allergic Diseases (hereinafter, the "basic law") came into force in June 2014,[3] and the Basic Guideline for Promoting Measures Against Allergic Diseases was announced in March 2017.[4] These pioneering national efforts are quite indispensable because one out of two people in Japan still have some form of allergic and/or immunological disorders.[5] Patients with these diseases show long-lasting phenotype(s), often repeating exacerbations and remissions, and with potential fatality, such as, anaphylaxis and severe drug hypersensitivity.

In addition, the "cross-sectional" problem lies in the measures against the diseases of which symptoms occur in various organs including the eyes, ears, skin, nose, kidney, respiratory organs, gastrointestinal organs, and central nervous system. Multiple different departments must thus be involved in the examination of patients, meaning that the close communication necessary for producing high-level study results is somewhat hard to achieve. Another hurdle for allergic and immunological diseases is the "vertical" problem concerning allergic march, a characteristic state in the progression and transition of various allergic diseases. Departments that examine these patients will change over time along with their growth and symptoms, and consequently, cohort-type studies are quite hard to accomplish. Furthermore, data and sampling methods for "big data" analysis have not been standardized, domestic cooperation is currently insufficient, and international harmonization is almost nonexistent. Due to differences in the characteristics of patients with allergic and immunological diseases between Westerners and Asians,[6] research and development (R&D) results presented in the European and North American literature must be applied carefully to clinical practice in Japan.

Thus, we shaped our vision focusing on *MIERUKA* for the unmet needs and complex issues across different levels and miscellaneous stakeholders through national and international collaborative research, based on which effective measures could be taken for the society in which patients and public live long, healthy lives, at each individual life stage. We set three goals for doctors, dentists, veterinarians, and other medical professionals (nurses, pharmacists, nutritionists, and clinical laboratory technicians); basic and clinical research scientists, supporting research staffs, and pharmaceutical/medical device companies; food, healthcare, and home appliance manufacturers; and patients, their families, and the public to promote their active participation and spontaneous contribution. The basic law also stated the responsibilities of these stakeholders, who will be a large driving force.[3] Finally, to achieve the vision and goals, major actions are to be promoted with three key words: Preemptive Treatment, Interdisciplinarity and Internationality, and Life Stage. This review introduces the developmental process and details of *Strategy 2030*. This article is based on a Japanese review first reported in *Arerugi*.[7]

Developmental process and characteristics of *Strategy 2030*

To plan this *Strategy 2030* holistically and effectively, it was essential to precisely understand the state of the art and to prioritize globally extracted keywords and themes. The MHLW played a central role in specially organizing a planning group with its grant-in-aid and with cooperation from seven relevant academic societies: the Japanese Society of Allergology, the Japanese Society of Pediatric Allergy and Clinical Immunology, the Japanese

Dermatological Association, the Oto-Rhino-Laryngological Society of Japan, the Japanese Ophthalmological Society, the Japanese Respiratory Society, and the Japanese Society for Immunology. Two physicians/scientists were nominated from each society as collaborators of the planning group. As a general rule, these nominations included one from the professorial level (around the age of 55 years) and one from the emerging scientist level (around the age of 45 years), for continuous follow-up over the next 10 years. A research consortium including these research collaborators created the first report (Fig. 1).

Based on the convergence of domestic and foreign wisdom, the vision and three goals were established to perform three major actions (Fig. 2) and to promote spontaneous contributions by various national and international stakeholders in the industry, academia, government, and public. To accelerate the achievement, the MHLW founded the Investigative Commission to clarify the positioning of the strategy, collect opinions from patients, their families, and the public (Fig. 3), and finalized this *Strategy 2030*,[8] including 12 specific actions (Fig. 4), a first of its kind worldwide.

Actions I: Fundamental research for pathophysiological elucidation and innovative preemptive treatments

A fundamental platform for understanding and stratifying the diversity of allergic and immunological diseases is essential to facilitate efficient preemptive treatment for appropriate targets. Particularly, as recent microbiome research has revealed, it is an effective strategy for identifying novel targets for diagnosis and treatment, to focus on the relationship between external factors and host factors at interfaces such as the epidermis and mucosal surface. Cooperation across organs, specialized fields, and medical departments, and collaboration with engineering, science, agriculture, etc. will be promoted as well (Fig. 4).

I-1. Fundamental research for understanding and stratification of disease diversity

Allergic and immunological diseases have a variety of phenotypes and disease states, depending on the age of onset, severity, and prognosis. Thus, the natural course, responsiveness to standard therapy, and the rate of side effects vary greatly among studies on these diseases, and the reported findings are often irreplicable. Thus, stratification should be performed from a comprehensive perspective, including detailed phenotype analysis (deep phenotyping),[9] and an analysis of endotypes based on an understanding of the molecular network, rather than uniform biomarkers (endotyping).[10] During the process, it becomes necessary to standardize the diagnostic criteria and classification rule among different institutions to help advance research on pathophysiology and evaluate treatment efficacy. In addition, stratification of healthy individuals (selecting high-risk groups of "potential patients") is also required to implement precision medicine[11] and preemptive therapy, which will be described in the next section. Furthermore, the utilization of artificial intelligence (AI) in "big data" analysis and standardizing phenotypes in model organisms need to be promoted.

A large-scale birth cohort study under the Japan Environment and Children's Study[12] and a third-generation cohort study by the Tohoku Medical Megabank Organization[13] are currently being conducted in Japan. Stratification of patients based on phenotypes is being attempted by bringing together such clinical information databases. However, these approaches pose many problems regarding differences in information categories, terminology, diagnostic definition, or the completeness of the stored information. Thus, in collaboration with Action III-4 described later, it is indispensable to make full use of good practices in the rare disease realm, where national and international databases have been harmonized in a globally standardized format,[14] resulting in the confirmed diagnosis,

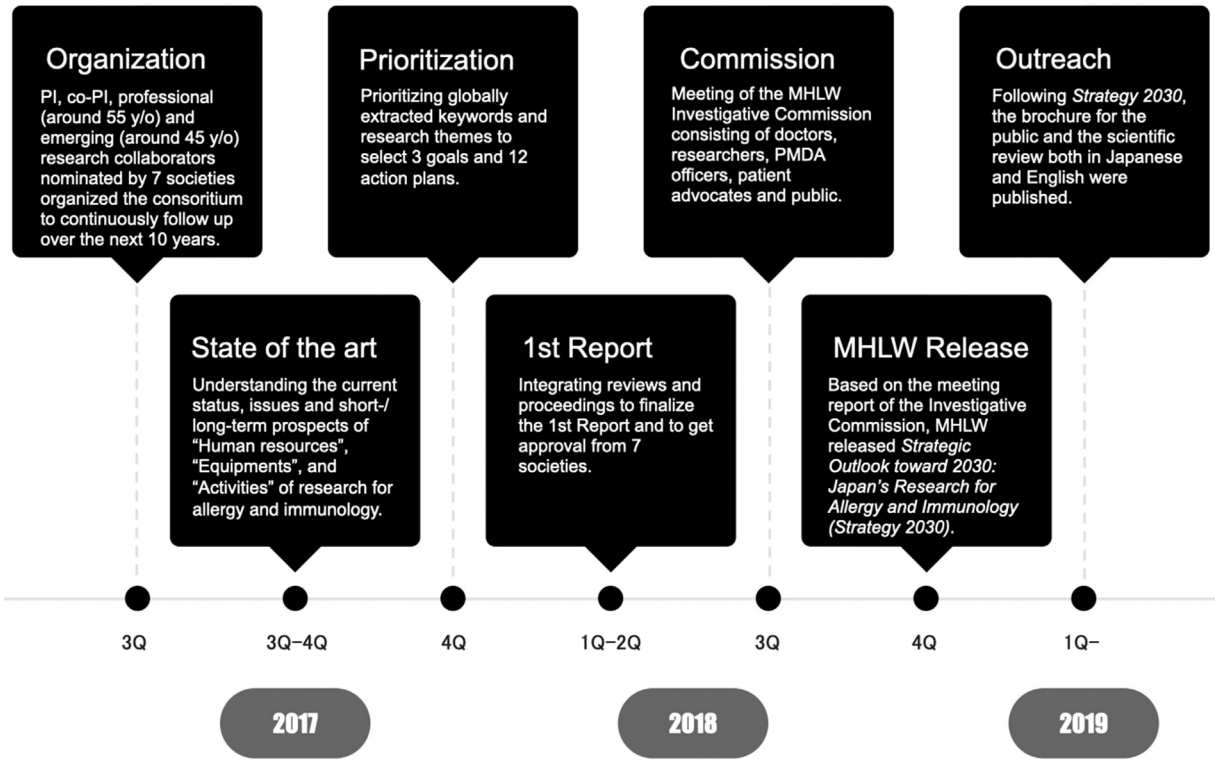

Fig. 1. Developmental process for Strategic Outlook toward 2030: Japan's Research for Allergy and Immunology.

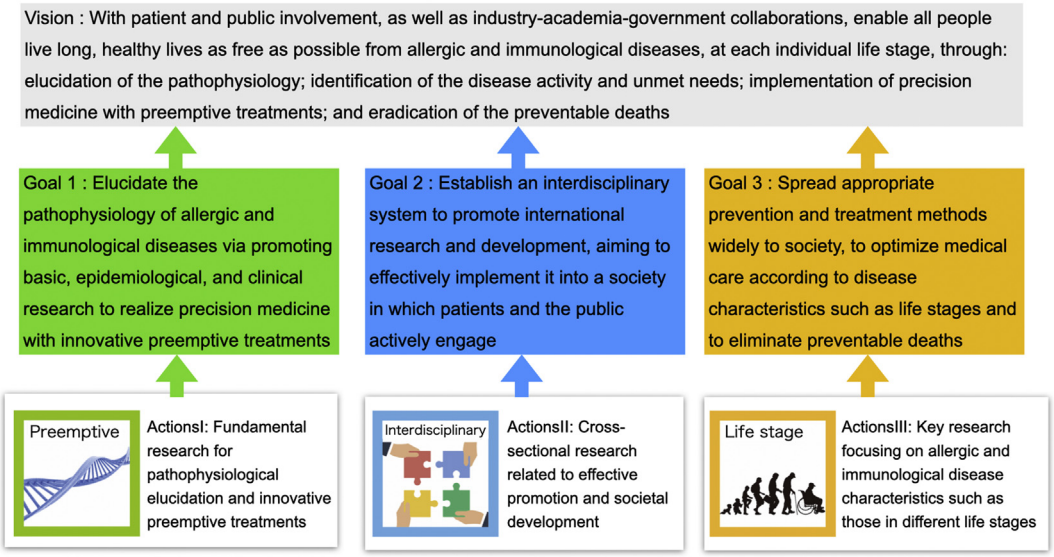

Fig. 2. Vision, goals, and actions of Strategic Outlook toward 2030: Japan's Research for Allergy and Immunology.

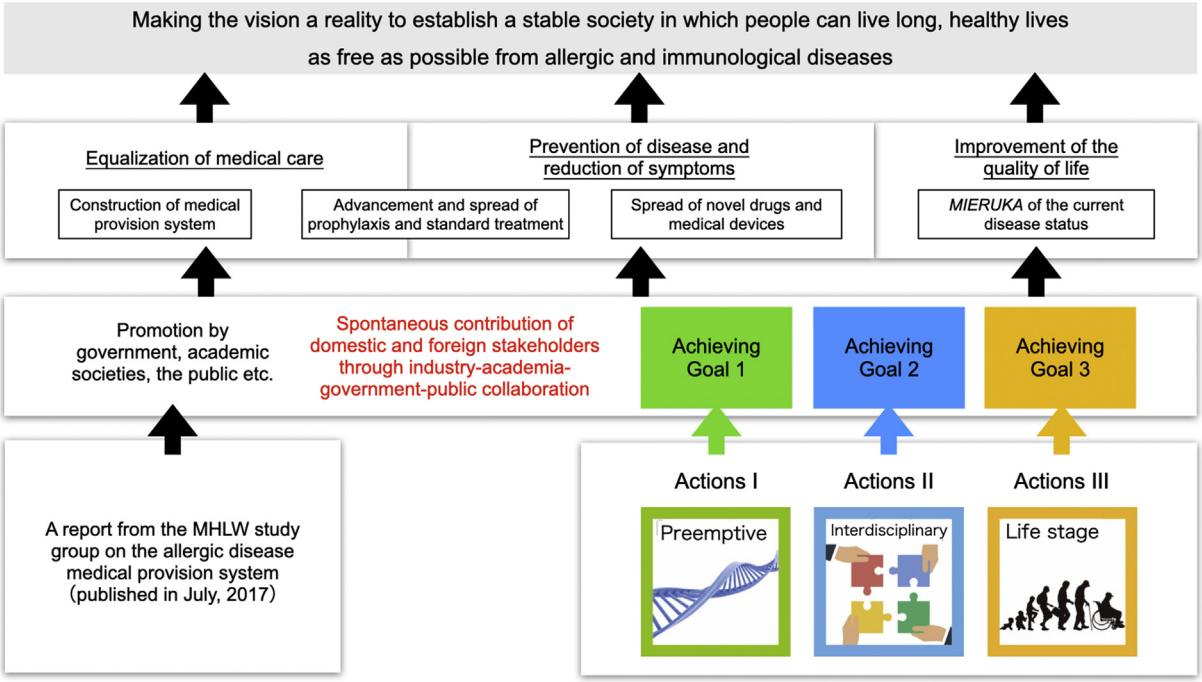

Fig. 3. Positioning of Strategic Outlook toward 2030: Japan's Research for Allergy and Immunology.

treatment and medical care.[15,16] With the standardization of clinical information and the deep phenotyping of patients with allergic and immunological diseases, multi-omics analysis of their samples from the peripheral blood, skin, and airway lesions, etc. would be promoted greatly. On the other hand, it is impossible to perform such multi-omics analyses in a single research laboratory or institution. Thus, the use of preexisting programs and closer cooperation among laboratories/institutions are essential.

I-2. Preemptive treatment R&D for future practical implementation of precision medicine

Whereas personalized medicine is a concept in which the best treatment method would be provided for each individual patient requiring high medical expenses, precision medicine groups patients into subpopulations who present the same specific symptoms, or those who are expected to respond to drugs in the same manner.[11] Treatment methods or disease prevention will be established for and delivered to each subgroup in precision medicine, with higher expected cost efficiency. Globally, many precision medicine initiatives have been launched to identify patient subpopulations for many immune-related multifactorial diseases.[11,17–20] However, these strategies have not clearly focused on specific patient populations. Thus, Action I-2 toward the regulatory approval of novel medical drugs and devices has to be promoted in collaboration with Action I-1, where subpopulations will be clearly determined by “screening” methods such as deep phenotyping or endotyping within patient populations or within a group of healthy individuals.

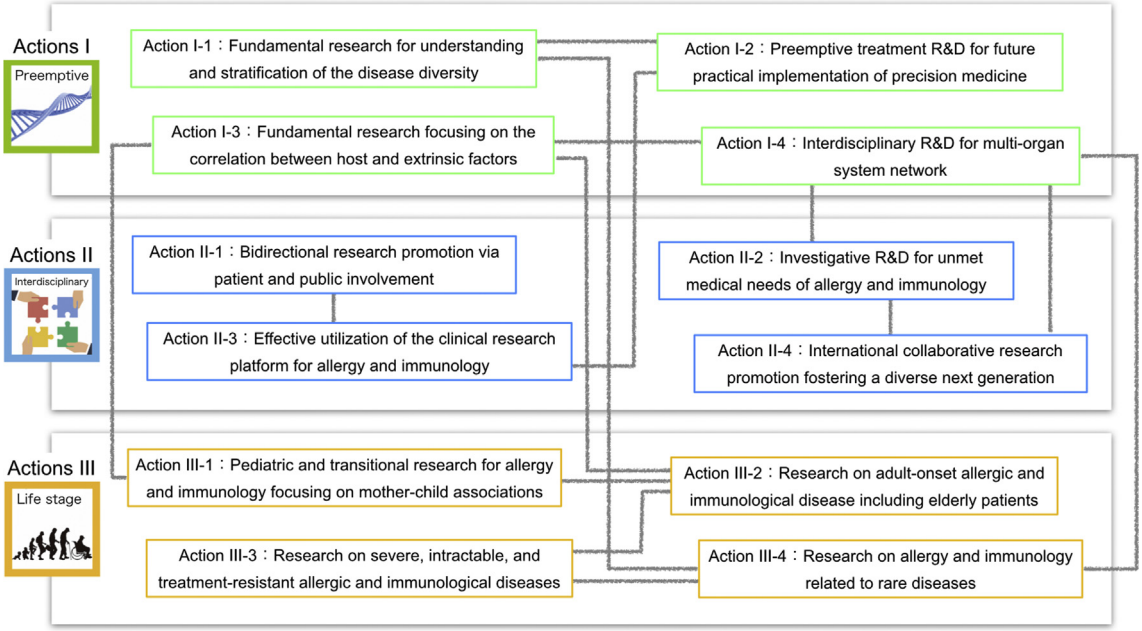

Fig. 4. Scheme of 12 actions of Strategic Outlook toward 2030: Japan's Research for Allergy and Immunology.

The approach of our country toward the practical use of disease multi-omics profiles the patients for early diagnosis, optimal treatment, and quick/precise prognosis and is generating many possibilities regarding preemptive therapy. It has been shown, for example, that the combination of thorough treatment of atopic dermatitis and early introduction of potential allergens is effective in preventing food allergies.[21] In addition, dysbiosis of the skin flora is reported to be involved in the onset of atopic dermatitis.[22] Amelioration of dysbiosis combined with strengthening of the barrier at the interface between the organism and the external world (e.g., skin, eyes, nose, and mouth) is expected to be important for preventing the onset of other immunological disorders that may follow. These measures may become key developmental strategies for preemptive therapy against allergic march. A recent study also suggested that anti-IgE antibody administration during pregnancy could lead to the prevention of allergy.[23]

Still, several difficulties in conducting academic research remain to be addressed in the development phase based on collaboration with pharmaceutical and medical device companies. Such difficulties include delayed timing for joining global clinical trials. It is necessary to clarify good practices for academic-industry collaborative R&D and its societal implementation when proceeding with Action I-2. Cooperation with Action II-3 described later is also needed for the effective utilization of a framework for conducting multicenter clinical trials in Japan and overseas.

I-3. Fundamental research focusing on the correlation between host and extrinsic factors

For stratification, which is essential for preemptive treatment R&D, it is important to elucidate the interaction between host factors, including immunological and genetic backgrounds, and various extrinsic factors at the interface. It has been reported that dysbiosis of the skin[22] or respiratory tract, smoking, exposure to air pollution and small particulate matter ($PM_{2.5}$), and susceptibility to specific viruses play important roles in the onset, progression, and increased severity of allergic and immunological diseases.[10,24–26] Of note, comparison of two groups of people (the Amish and Hutterites) who share a similar genetic background revealed that the risk of asthma was lower among the group that engaged in traditional farming compared to those who engaged in modernized farming.[27] In this case, the natural immune responses differed according to external factors (here, differences in farming style). Such studies with a new approach that incorporate external factors are gaining much attention and are to be encouraged. Making the most of the relatively homogeneous genetic background of the Japanese population, Action I-3 would promote comparisons and investigations of the diversity regarding lifestyle, weather, or seasons toward future breakthroughs.

Given the importance of results regarding locality- or age-related differences, data sharing and coordination with research using existing specimens and cohort studies are also essential. Ongoing studies conducted on donated blood samples stored by the Japanese Red Cross Society have revealed the regional and generational diversity of the allergen(s)-specific IgE positivity rate.[28] Furthermore, collaborative research involving housing, bedding, home electronics, food, beverage, and cosmetics manufacturers will be effective not only for creating a healthier internal environment of the body, but also for controlling external allergens (such as cedar pollen) where one often needs political measures as well.[29] Particularly, collaboration with Actions III-1 and III-2 focusing research on patients' life stage is of importance for comparison of generational differences.

I-4. Interdisciplinary R&D for multi-organ system network

Despite having many aspects in common regarding immunological mechanisms, neurological findings (for symptoms such as itching),[30] and barrier functions,[31] various symptoms in different organs have prevented interdisciplinary R&D regarding the multi-organ system network beyond the medical department boundaries in Japan. Several countries set up their registration systems for individual diseases at the national level, and many epidemiological study results that utilized such databases have been reported.[32] Furthermore, it is important to collect objective data that may be useful within different clinical fields and to standardize the data for

furthering research that goes beyond the borders of individual organs. For example, asthma is often diagnosed subjectively via auscultation among doctors, although the findings must be transformed into objective data.[33] Such interactions between different fields will be essential for driving forward R&D beyond the borders, which would be promoted by Action I-4, in collaboration with Action I-3 for improving the environment inside and outside the body; Action II-2 for investigative R&D for unmet medical needs utilizing apps, wearable devices, and AI; and Action II-4 for international cooperation and human resource development.

Of note, many advanced results on allergic and immunological research have been reported as a result of information sharing from basic to clinical research. In addition to promoting translational research, a future issue will be how to proceed with "reverse translational research", which links questions arising in daily clinical practice to basic research. Thus, building a sustainable collaborative platform is extremely important in reference to pioneering strategies in the rare disease field described later in Action III-4.

Actions II: Cross-sectional research related to effective promotion and societal development

Effective promotion of allergic and immunological research requires the establishment of cross-sectional infrastructure that incorporates new perspectives and new participants. Actions II focus on four areas: patient and public involvement (PPI), *MIERUKA* of unmet needs, clinical research infrastructure including central ethics review, and promotion of international collaboration (Fig. 4).

II-1. Bidirectional research promotion via patient and public involvement

Since the 2000s, a system has been established so that patients and related patient organizations and civil society groups could participate in the design, conducting, and reporting of clinical studies in several countries including the UK.[34] It has been increasingly understood that designing clinical trials with patient input is useful for improving the quality and speed of research.[35] In these discussions, the importance of their active participation in research has become clear, apart from the issues on subject protection. It was also clarified that it is important to educate groups that cover multiple diseases rather than focus on a single disease (area).[36] Action II-1 aims to clarify the appropriateness of the PPI in Japan's allergic and immunological research for the study design, execution, and report of clinical research and trials in the platform promoted by Action II-3.

In the realm of allergy and immunology in Japan, the PPI is insufficient compared to other pioneering realms, including cancer and rare disease. However, some patient and public organizations with statuses of general incorporated associations or non-profit organizations are actively engaged in providing appropriate medical information and providing patient education in cooperation with healthcare professionals.[37] There is a need for an information network in which appropriate information is quickly transmitted to the public, not only for lifestyle management including clothing, food, and shelter, but also for PPI.

II-2. Investigative R&D for unmet medical needs of allergy and immunology

Unmet medical needs for allergic and immunological research include the discrepancy between clinical guidelines and on-site medical care, the accurate prediction of the start date of pollen scattering, the optimization of disease and complication management, and the establishment of team medical care.[38,39] It has also been pointed out that it is difficult to evaluate the results of research on allergic and immunological diseases because of poor indicators for objectively evaluating disease activity and life satisfaction. Furthermore, it is necessary to investigate these medical and social needs comprehensively and evaluate them together with host and external factors of patients; otherwise, the *bona fide* unmet medical needs cannot be identified.[32,40–42]

To verify the future effects of *Strategy 2030*, Action II-2 would promote research to create indicators of *MIERUKA* for disease activity and life satisfaction. To this end, in connection with Actions I-4 and II-4, it is desirable to work with diverse stakeholders, including industries, to develop apps and wearable devices that can comprehensively collect data regarding patient needs, as well as to promote the utilization of AI technology. It is also important to promptly reflect the needs of patients detected by such collaboration between industry, academia, government, and private sectors into basic/clinical/policy research.

II-3. Effective utilization of the clinical research platform for allergy and immunology

Multicenter clinical studies/trials are considered the gold standard method for recent medical evaluation. With increasing size and complexity of the research, the burdens on institutional review boards (IRBs) and on clinical investigators seeking IRB review increases. Thus, review by the centralized IRB (CIRB) is being promoted worldwide to facilitate rapid patient-centered ethics reviews. This review is aimed at guaranteeing coherence of reviews in observational studies in which multiple institutions participate, and to avoid inconsistent reviews based on ethics decisions that are not in line with actual clinical practice. In the United States, collective review has become obligatory under the revised Common Rule.[43] Collective review has also been obligated in the UK since 2004 based on the EU Clinical Trial Directive/Regulations.[44] In Japan, a collective review is permitted in the Ethical Guidelines for Medical and Health Research Involving Human Subjects[45] and in the Ethical Guidelines for Human Genome/Gene Analysis Research.[46] Standardization of review quality and improvement of the efficiency of the review are being developed via smooth implementation of the CIRB.

Currently, to accelerate high-quality clinical research indispensable to the development of innovative pharmaceuticals and medical devices from Japan, Core Clinical Research Hospitals, which play a central role in national and international clinical research and in investigator-initiated clinical trials are being developed, to also provide the necessary support for other medical institutions.[47] Regarding allergic and clinical disorders, the maintenance of medical provision systems is being promoted in each jurisdiction, to establish the allergic disease medical core hospitals.[48] Action II-3 will actively collaborate with and effectively utilize the CIRB in these core hospitals to promote the preemptive treatment R&D in Action I-2.

II-4. International collaborative research promotion fostering a diverse next generation

It has been reported in recent years that the pathophysiology of allergic and immunological diseases may differ between Europeans and Asians.[6] Thus, study results presented in European and North American literature must be applied carefully to clinical practice in Japan. Also, in the Japanese medical system, medical specialists see patients from the beginning, unlike in Europe or North America, where general practitioners play a central role in primary care. An accurate diagnosis and precise approaches to patients with specific diseases are generally guaranteed at a very early stage in our

system. However, such differences between Japan and other countries are not sufficiently disseminated in the English language to the international community. Lack of information on the current state of Japan, including disease prevalence, poses some risk that may make it difficult for Japan to engage smoothly in international collaborative research or clinical trials. Furthermore, the number of internationally co-authored papers with high impact from Japan has been relatively declining, as reported by the Shibayama Initiative of the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT).[49]

Herein, Action II-4 would promote the construction of a sustainable platform fostering scientists who will bridge Japan and other countries and play an active part in the world without bias regarding age, sex, or ethnicity to increase the international presence of Japan. Academic societies would lead these efforts beyond their borders, especially in forming a task force composed of emerging researchers. Global human resource exchange and international collaborative research will be promoted between universities and research institutions with such a platform, so that young scientists would actively participate in international programs such as the Human Frontier Science Program (HFSP)[50], and the Interstellar Initiative presented jointly by the Japan Agency for Medical Research and Development (AMED) and the New York Academy of Sciences.[51] Needless to say, it is also important to strengthen the dissemination of information in English on the state-of-play of allergic and immunological research, development, and medical care in Japan.

Actions III: Key research focusing on allergic and immunological disease characteristics such as those in different life stages

One of the most important characteristics of allergic and immunological diseases is that the disease and condition change with the transition from the mother to the baby, infant, adolescent, adult, and elderly. In addition, it is necessary to focus on research regarding severe, intractable, and refractory diseases and on those with a small number of patients. Zeroing “preventable deaths” in some severe allergic and immunological diseases is a key goal of *Strategy 2030*, aimed at optimizing medical care and disseminating preventive and therapeutic methods according to these disease characteristics.

III-1. Pediatric and transitional research on allergy and immunology focusing on mother–child associations

Allergic and immunological diseases are thought to be a result of complicated interactions between genetic predisposition and epigenetics reflecting environmental factors, including those that occur during gestation. Particularly, environmental factors pertaining immediately after birth; feeding practices, including breastfeeding and weaning; and the development of skin barrier function in early infancy that affects skin sensitization are all likely to affect life-long allergen sensitization and the subsequent development of allergic diseases.[21,52–57] The presence of allergic march, a process in which an allergic disease that starts as atopic dermatitis during infancy later develops into food allergies, bronchial asthma, allergic rhinitis, or conjunctivitis over time during childhood suggests the importance of promoting research focusing on the successive characteristics of allergic and immunological diseases, including mother–child associations.

Action III-1 will cooperate with Actions I-3 and III-2, to drive comprehensive analysis of genetic and environmental factors related to the onset of allergic and immunological diseases using data and samples from preexisting cohort studies, including information from mothers as much as possible. Studies on disease pathophysiology using appropriate model organisms will also be promoted. Advanced Research & Development Programs for Medical Innovation (AMED-CREST, PRIME) have promoted cutting-edge R&D in the specific area designated by MEXT. The program launched the novel area in 2019, to develop a comprehensive understanding of various biological phenomena at the early stage of life,[58] where innovative synergy is expected with *Strategy 2030*. By identifying high-risk group(s) of patients and/or their families extracted from the analysis as well as the preventive measures for that group, scientific information will be provided to potentially reduce the prevalence of allergic and immunological diseases.

III-2. Research on adult-onset allergic and immunological disease including elderly patients

Some allergic and immunological diseases, including bronchial asthma, rhinitis, sinusitis, contact dermatitis, and drug hypersensitivity often show adult-onset symptoms that are also found in the elderly.[59,60] The adult-onset group of atopic dermatitis patients also has different characteristics.[61] In contrast to childhood atopic-type allergies, in which type-2 cytokines and IgE are the primary actors, adult-onset allergies have complicated disease states with multiple causative factors, such as age-related changes in skin and mucosal barrier functions or immunosenescence. Allergic diseases are often more severe or fatal in adults compared to children and have characteristics such as exacerbation despite responsiveness to systemic steroid administration. An example of this is allergy-related severe respiratory disorder, which develops from aspirin-exacerbated respiratory disease (AERD) or allergic bronchopulmonary mycosis (ABPM). Thus, measures aimed at combating these diseases are required urgently.

Studies on aging are being conducted actively worldwide. AMED-CREST has launched its novel research area to clarify the mechanisms underlying functional impairment among individuals over their lifetime.[62] The Nature Partner Journals *Aging and Mechanisms of Disease* has also been launched recently.[63] On the other hand, a comprehensive analysis of adult-onset allergies is not sufficient both domestically and internationally. Thus, Action III-2 will collaborate with Actions III-1 and III-3 to promote comprehensive and cross-sectional studies on the natural course of adult-onset allergic and immunological diseases. Clustering of adult-onset allergies will be attempted. Collaboration will be initiated with basic researchers, including *in vivo* analysis using animal models, and the analysis of the mechanisms underlying age-related changes or immunosenescence.

A recent Japanese study conducted among supercentenarians, rare individuals who live for more than 110 years, have revealed that they have unique immunological characteristics in their circulating lymphocytes via single-cell transcriptome analysis.[64] Such unique studies conducted in Japan, a society aging at a globally unprecedented pace, may allow us to eventually lead other countries in this research field.

III-3. Research on severe, intractable, and treatment-resistant allergic and immunological diseases

Approximately 50–70 fatalities occur due to anaphylaxis per year in Japan. The most common causative allergens reported are pharmaceutical drugs. The fatality rate of toxic epidermal necrolysis, which is known to be one of the most severe drug allergies, is reported to be between 20 and 40 percent.[65] Drug-induced hypersensitivity syndrome (DiHS) is a type of severe drug eruption, and its concept as a disease originated from Japan. Recent accumulating studies have revealed some cases of death due to

complications of autoimmune diseases during the course of DiHS.[65] Despite the widespread use of epinephrine autoinjectors in recent years, fatalities resulting from anaphylaxis induced by food allergens have not been eliminated.

Herein, Action III-3, in cooperation with Action III-2 and III-4, will promote research to elucidate the long-term pathophysiology of severe, intractable, and treatment-resistant allergic and immunological diseases and the effects of each life stage. Specifically, the details of preventable symptoms, complications, and/or relapse will be investigated from studies on natural history. It is also important to clarify the safety, efficacy, and cost of novel treatments such as allergen immunotherapy and biologics. The systematic dissemination of evidence necessary for proper use of these treatments is expected to contribute to the societal implementation of standard treatment for severe and intractable allergic and immunological diseases from childhood to adulthood, and to zero the number of "preventable deaths" (deaths among patients due to lack of proper medical management).

III-4. Research on allergy and immunology related to rare diseases

Analysis of the pathophysiology underlying rare genetic disorders is an important R&D strategy in searching for innovative R&D seeds for common diseases, including allergic and immunological diseases. Given the success of the transformation of R&D from the rare diseases area to common diseases, such as, the anti-RANKL monoclonal antibody (from osteopetrosis to osteoporosis), PCSK9 inhibitor (from familial hypercholesterolemia to hyperlipidemia), and SGLT2 inhibitor (from familial renal glucosuria to diabetes), not only startup companies but also many large pharmaceutical companies have taken on their efforts on this scheme. R&D on rare diseases is also promoted by the Food and Drug Administration (FDA),[66] European Medicines Agency (EMA),[67] and the MHLW and Pharmaceuticals and Medical Devices Agency (PMDA) in Japan.[68,69]

Other pioneering strategies in this realm are the Initiative on Rare and Undiagnosed Diseases (IRUD)[15,16] and the Rare Disease Data Registry of Japan (RADDAR-J).[70] Patient data registration in the Human Phenotype Ontology format has been standardized[14] and has already contributed greatly to diagnosis, treatment, and medical care, in combination with the maximum output from next generation sequencing. Dozens of new diseases have been already identified for the first time globally. To link the questions of IRUD clinicians to basic research, a "reverse translational research" platform (the Japanese Rare Disease Models and Mechanisms Network (J-RDMM)) has been developed on functional analysis of genetic variants.[71] The network is developing the international consortium for utilizing related model organisms.[72]

Action III-4 will promote collaboration with and effective utilization of these rare disease strategies, aiming to increase the number of R&D seeds and to identify novel therapies from developmental paths that are different from those in the past. These collaborations are expected to contribute not only to bilateral R&D promotion between the allergic and immunological realm and rare disease, but also to other disease realms as an important role model.

Future perspectives

Basic immunological research conducted in Japan has made great discoveries, such as those regarding IgE and its allergic pathogenesis,[73] immunoglobulin gene rearrangement,[74] and the immune checkpoint system.[75] To build on and advance these historical achievements further, this paper, titled *Strategic Outlook toward 2030: Japan's Research for Allergy and Immunology*, was formulated to focus on diversity and interdisciplinarity, in hopes that it will be of interest not only to researchers but a broader readership in Japan and beyond, strengthening international cooperation. To achieve our goals, it is essential to make effective use of our limited research resources (human, financial, and time), drawing on the efforts of all stakeholders and the unique R&D ecosystem in Japan, and cooperating with relevant societies, including the Japanese Society of Allergy. In the next 10 years, it is also indispensable to understand the grand design of global research for allergy and immunology and the evolution of patient and public needs, which will be re-evaluated in the mid-term review. Needless to say, re-investigation of the state of the art in immunology and allergy and re-adjustment of the strategy are necessary for a sustainable platform.

Research in the fields of allergy and immunology aims at contributing toward a stable society in which people can live long, healthy lives at each life stage. We believe that in fulfilling our ambitious vision, goals, and actions over the next 10 years, not only will Japan become a world leader in the life sciences and technology, but will contribute toward the wellbeing of patients suffering from allergic and immunological diseases and their families, and advance knowledge in other areas of disease for the benefit of the nation as a whole.

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Conflict of interest

Advisory role: SF, GlaxoSmithKline, Kyowa Kirin, Sanofi. **Honoraria:** KA, Astellas Pharma, AstraZeneca, Nippon Boehringer Ingelheim, GlaxoSmithKline Consumer Healthcare Japan, Novartis Pharma; EU, Santen Pharmaceutical, Senju Pharmaceutical; MO, Mitsubishi Tanabe Pharma, Taiho Pharmaceutical; HS, Mitsubishi Tanabe Pharma, Taiho Pharmacetutical, Novartis Pharma, Maruho, Torii Pharmaceutical, Sanofi, Kyowa Kirin, Eli Lilly Japan, Otsuka Pharmaceutical, AbbVie, Celgene; MN, Novartis Pharma; NH, GlaxoSmithKline, AstraZeneca, Nippon Boehringer Ingelheim, Novartis Pharma; AF, Santen Pharmaceutical, Senju Pharmaceutical, Novartis Pharma; SF, Kyorin Pharmaceutical, Taiho Pharmaceutical, Mitsubishi Tanabe Pharma, Torii Pharmaceutical, Sanofi, MSD. **Manuscript fee:** AF, Santen Pharmaceutical. **Research funding:** MA, Maruho, Torii Pharmaceutical, Sanofi, Taiho Pharmaceutical, Kyowa Kirin, Kose; KA, Novartis Pharma, Sanofi, Kyorin Pharma; KKab, Japan Tobacco, Mitsubishi Tanabe Pharma, Torii Pharmaceutical, Sun Pharma Japan (Pola Pharma), Eisai, Taiho Pharmaceutical, Ono Pharmaceutical; SK, Nippon Boehringer Ingelheim, AstraZeneca, Kyorin Pharmaceutical, Actelion Pharmaceuticals Japan, Novartis Pharma, Chugai Pharmaceutical; HS, Tokiwa Pharmaceutical, Maruho, Torii Pharmaceutical, Kyowa Kirin, Taiho Pharmaceutical, Eisai, Mitsubishi Tanabe Pharma; NH, GlaxoSmithKline, Nippon Boehringer Ingelheim, Novartis Pharma, MSD, Ono Pharmaceutical, Daiichi-Sankyo; AF, Santen Pharmaceutical; SF, Maruho, Tsumura, Mitsubishi Tanabe Pharma, Sanofi; KY, Takeda Pharmaceutical, Chugai Pharmaceutical. The rest of the authors have no conflict of interest.

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