



CONNECTING PEOPLE, CHANGING LIVES.



Japan Agency for Medical Research and Development

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WE ARE AMED, THE JAPAN AGENCY FOR MEDICAL RESEARCH AND DEVELOPMENT.

Making life better for patients
around the world today.

*“Our mission is to fast-track medical
research and development.”*

As medicine continues to advance at a remarkable rate, the development of new approaches to diagnostics and therapeutics to contribute to human health is vital. Under the growing weight of public expectation, we must continually face new challenges while trying to solve public health problems.

AMED was established in April 2015 to catalyze the process of medical innovation and overcome the barriers between sectors, connecting talented individuals to accelerate medical research and development.

In just three years, we have made significant gains in the fight against many diseases.

As part of the Initiative on Rare and Undiagnosed Diseases (IRUD), genetic analysis systems are more accessible than ever. This is thanks in part to the data sharing among physician scientists in Japan, which was pioneered by AMED. Through IRUD and the study of genetic analysis, 12 new diseases have also been discovered. More than 800 undiagnosed patients who suffered from diagnostic odyssey over many years were diagnosed within 6 months after their registration to the program. IRUD is now contributing to several case matching between Japanese and foreign patients, as AMED empowers global networks for data sharing.

In addition, we are in constant pursuit to solve Antimicrobial Resistance (AMR) – an issue that poses significant threat to the world. The Japan Nosocomial Infections Surveillance (JANIS) program, which facilitates AMR data sharing between hospitals, will soon be introduced to Southeast Asian countries.

Furthermore, as Japan moves towards a super-aging society, we made it our mission to build up a nationwide registry to assist with and contribute to dementia research and drug development.

AMED is also interested in reforming and galvanizing the funding systems. Beginning last year, we initiated Cyclic Innovation for Clinical Empowerment (CiCLE), a large-scale program in pursuit of greater medical innovation that fosters human resources. Under a collaborative effort between industry and academia, the program will run for a maximum of 10 years and provide participants the opportunity to develop into talented young leaders – those who can help us progress into the future.

While our progress is encouraging, we understand the challenges we face cannot be overcome without global collaboration. To date, we have entered into Memorandum of Cooperation agreements with several of our counterparts: NIH in the U.S., MRC in the U.K., A*STAR in Singapore, SEIDI in Spain and the Ministry of Health in Lithuania. We have also established offices in the U.S., U.K. and Singapore to further reinforce our relationships.

Many challenges lie ahead as we work to improve health in Japan and around the world. However, through close cooperation with the global medical community, we can deliver the best medicine and change lives for the better.



Makoto Suematsu, M.D., Ph.D.
President, AMED

Who We Are

The Japan Agency for Medical Research and Development (AMED) was established in 2015 for the advancement of medical discoveries that make life better for everyone.

Based on effective partnerships and innovative collaboration, we pursue medical breakthroughs through an approach consisting of three vital components:

- 1

SUPPORT
Funding medical studies and research facilities
- 2

CONNECT
Linking organizations, institutions and researchers
- 3

PROMOTE
Promoting the practical application of beneficial research outcomes

People are at the heart of everything we do. We support, connect and promote, helping researchers to make incredible discoveries and change the lives of patients around the globe.

HEADQUARTERS FOR HEALTHCARE POLICY (HHP)



Japanese government establishes top-level policy for medical research and development.

What We Do

Working beneath the Prime Minister's Cabinet and national ministries, we provide a single window for researchers and institutions seeking funding for medical research and development.

Prior to our establishment, researchers were required to request funding from several ministries, depending on the phase of their studies. Now, we provide streamlined, consistent support from initial investigations to practical application of new medicines and treatments in the real world.

We also work to connect the most qualified practitioners, medical institutions and private-sector organizations, at home and abroad, to give clinical studies the best possible chance of succeeding.

Once studies are completed, we focus our resources on promoting new medicines and treatments to ensure they get to the people who need them most.

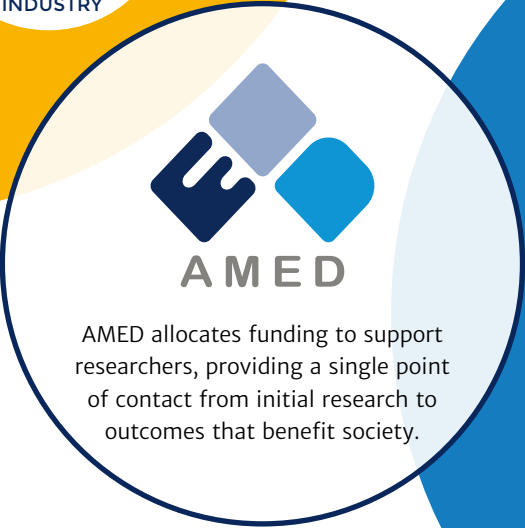
When it comes to medical innovation, we are with you every step of the way.

A New Approach to Medical Research & Development

In line with government policy, we provide a single window of support and funding for research projects.

JAPANESE GOVERNMENT MINISTRIES

Ministries establish mid/long-term goals based on government policy and set budgets accordingly.



RESEARCHERS AND INSTITUTES



FUNDING ALLOCATION BY AMED

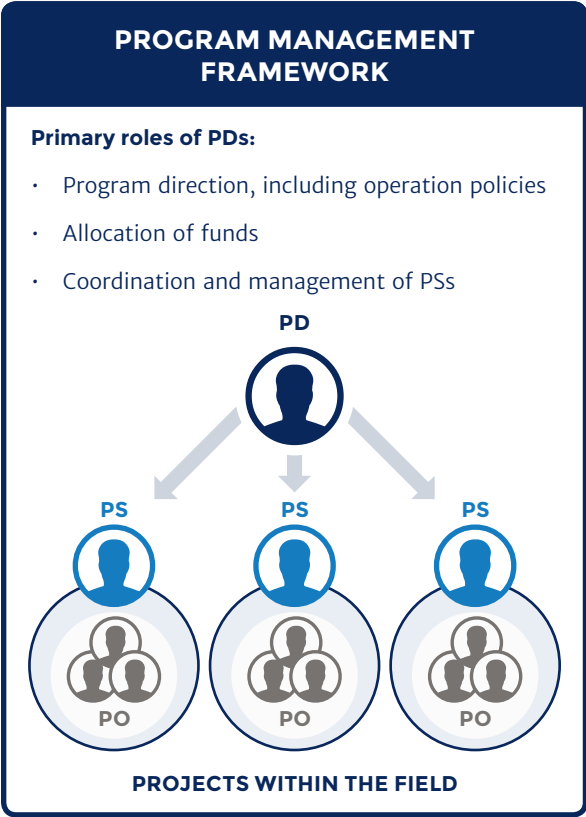
In addition to funding allocation, AMED networks academia and industry in order to accelerate medical discovery.

Management and Evaluation Framework

To ensure the best chance of beneficial research outcomes, we assign program directors (PD) to each of our nine key fields, and program supervisors (PS) and program officers (PO) to each program within the field.

These individuals have distinguished academic backgrounds and

are handpicked for their expertise in a specific area of research. They work closely to grasp the situation and challenges in their field in order to comprehensively evaluate research proposals and provide expert program coordination. Their ultimate goal is to manage research and advise researchers to make processes run more smoothly and ensure better results.



Our PDs offer expert insight into key strategic fields of research. In addition to promoting collaboration between related fields, PDs monitor entire grant programs and make expansion and acceleration recommendations to AMED.



Our PSs possess a precise understanding of the aims and challenges related to their respective programs in order to effectively oversee operation.

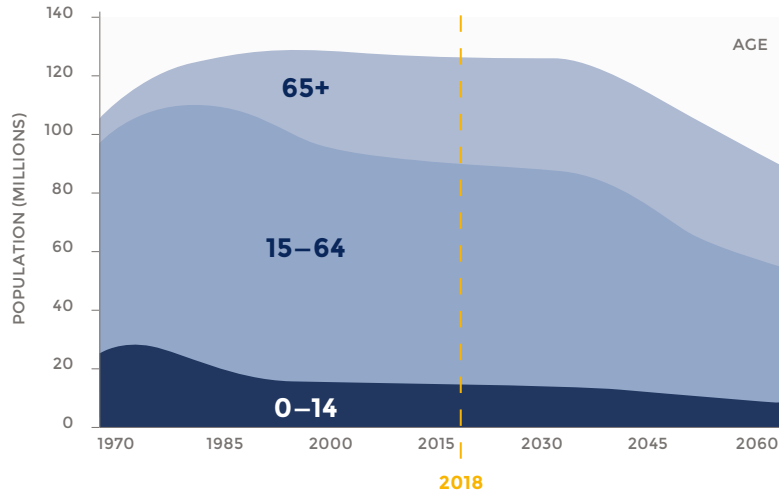


The role of our POs is to assist PSs, taking responsibility for day-to-day program administration.

Our Challenges

Like the rest of the world, Japan continually faces new and urgent public health challenges. The emergence of infectious diseases and prevalence of chronic conditions require constant attention, but perhaps the most significant challenge is the country's aging population. Our government has defined its strategy to address this challenge, citing cutting-edge medical technology and care as vital to the creation of a society that enjoys longer, healthier lives. AMED is striving to meet this challenge head-on.

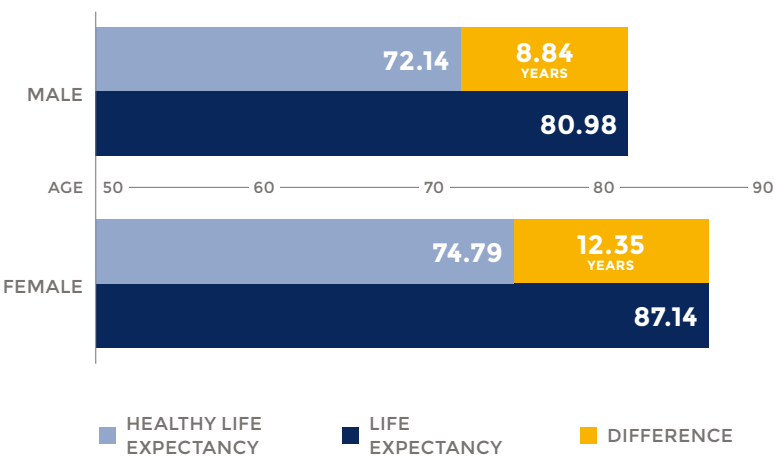
Population Structure (Japan)



NATIONAL INSTITUTE OF POPULATION AND SOCIAL SECURITY RESEARCH

Our population is aging faster than that of any other nation. The percentage of those over 65 years old increased from 7.1% in 1970 to 26.7% in 2015, and it is predicted to reach 38.4% by 2065. As a result of this shift, the burden on our national healthcare system is greater than ever. That's why finding effective solutions is one of our top priorities.

Life and Healthy Life Expectancy (Japan)



2016 MINISTRY OF HEALTH, LABOUR AND WELFARE DATA

Life expectancy in Japan is among the longest in the world. However, the difference between life and healthy life expectancies stands at 8.84 years for males and 12.35 years for females. To shorten the gap, we focus on making discoveries that allow people to enjoy longer, healthier and more active lives.

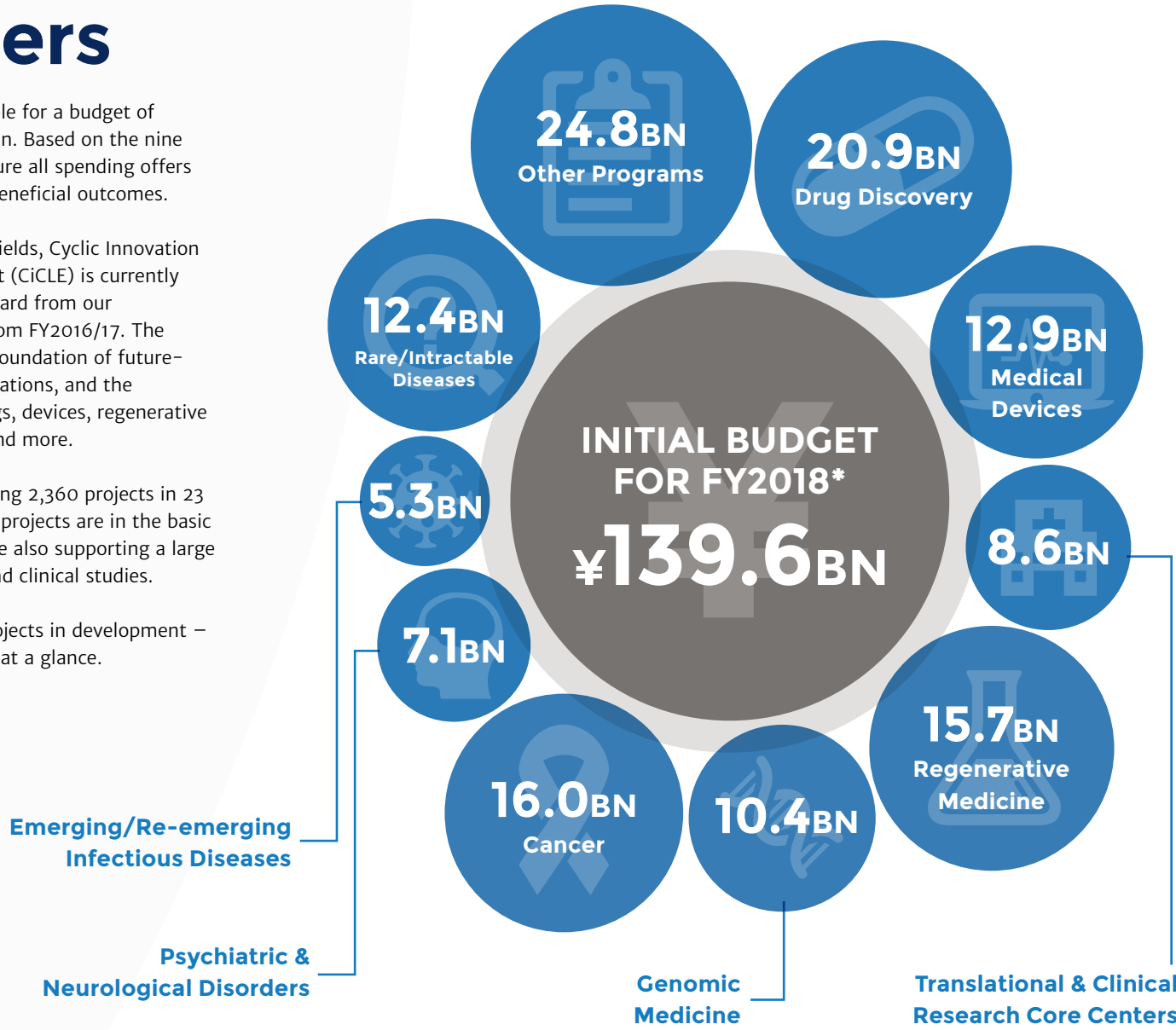
Our Work in Numbers

In 2018, we are responsible for a budget of approximately ¥139 billion. Based on the nine key fields, we aim to ensure all spending offers maximum potential for beneficial outcomes.

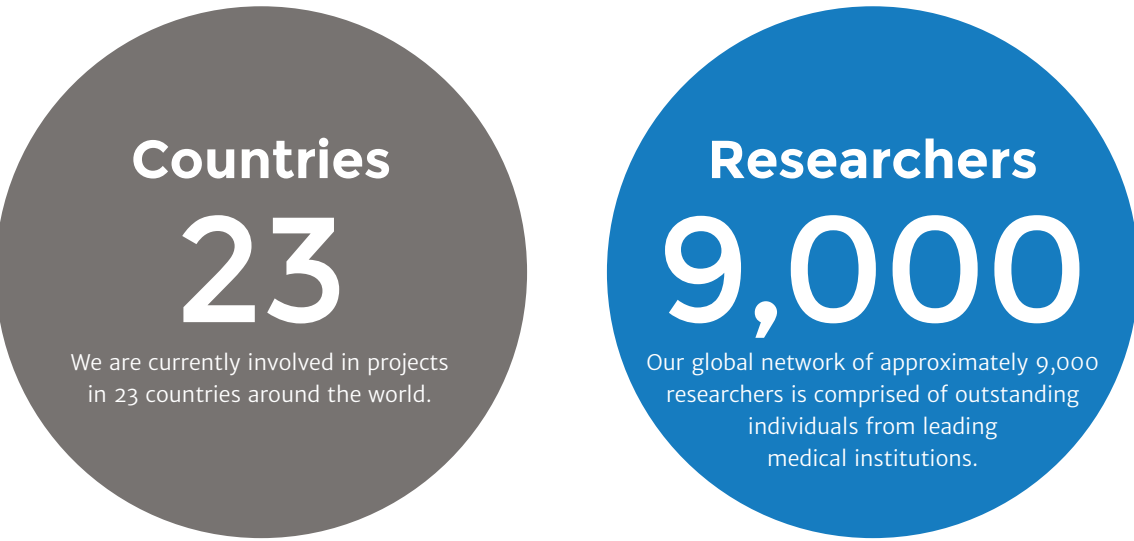
In addition to these key fields, Cyclic Innovation for Clinical Empowerment (CiCLE) is currently active, but is carried forward from our supplementary budget from FY2016/17. The program focuses on the foundation of future-generation medical innovations, and the development of new drugs, devices, regenerative medicine, technologies and more.

We are currently supporting 2,360 projects in 23 countries. Many of those projects are in the basic research stage, but we are also supporting a large number of pre-clinical and clinical studies.

Budget allocation and projects in development – all of AMED’s key figures at a glance.



*SOME BUDGET ALLOCATIONS OVERLAP; FIGURES IN JPY
2018/19 DATA



FY2017 DATA

Grant Programs

We promote leading-edge medical innovation from discovery and development to clinical application. Focused on nine key fields, everything we do is guided by the Japanese government's Plan for Promotion of Medical Research and Development.

Our projects are solicited through wide-ranging calls for proposals, which are aimed at outstanding individuals working in world-class institutions. Our role as custodians of public money means we consider each proposal thoroughly in order to

maximize the potential for beneficial outcomes.

Once projects are launched, we work to create the conditions necessary for discovery, establishing framework and putting together teams of distinguished researchers.

But our work does not stop there. We continue to support projects at every stage of their journey to ensure everything we do is underpinned by the highest quality and integrity.

DEPARTMENT

Research Promotion

- Division of Regenerative Medicine Research
- Division of Cancer Research
- Division of Neurological, Psychiatric and Brain Research
- Division of Rare/Intractable Disease Research
- Division of Infectious Disease Research

Industrial-Academic Collaboration

- Division of Medical Device Research
- Division of Industrial-Academic Collaboration

International Affairs

- Division of International Collaboration

Research Infrastructure

- Division of Biobank
- Division of Emerging Research

Clinical Research & Trials

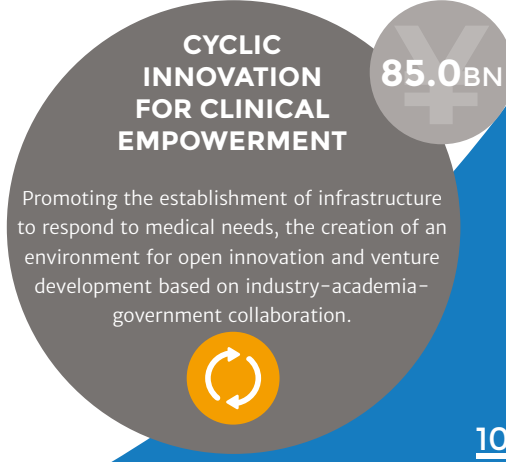
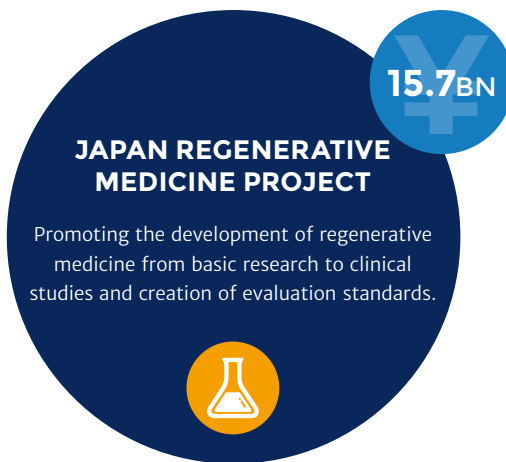
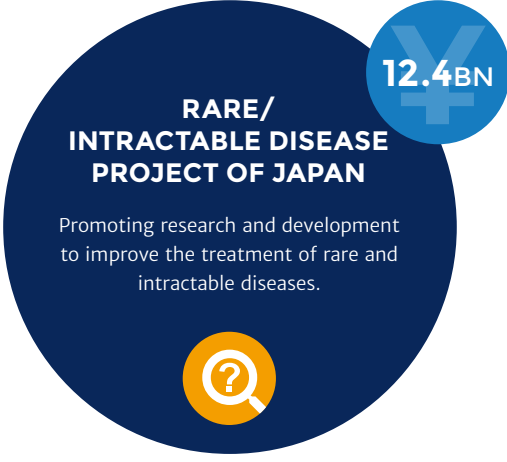
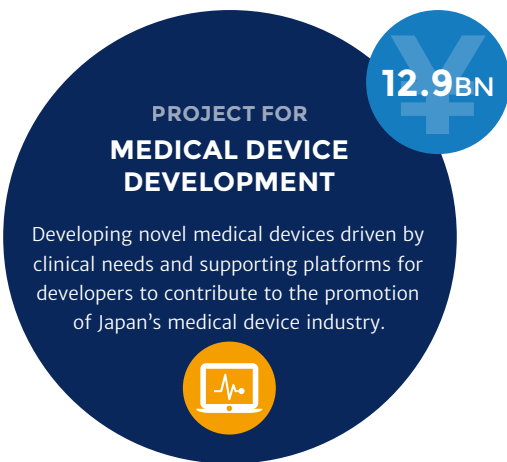
- Division of Clinical Research and Trials

Innovative Drug Discovery & Development

- Division of Strategic Planning & Evaluation
- Division of Drug Research
- Division of Regulatory Science

Cyclic Innovation

- Department of Cyclic Innovation



International Collaboration

At AMED, we understand that improving quality of life for people around the world is a global effort. That's why we adopt an international approach, contributing Japanese expertise and actively engaging in research and development activities in collaboration with our counterparts around the world.

Bases of Cooperation

Recognizing the importance of international collaboration and cooperation, we have established three overseas offices in Washington, D.C., London and Singapore. Their missions are to develop networks with overseas funding agencies, institutions, universities, scientists and researchers; promote overseas joint research and development programs; and collect and disseminate the latest information on medical science and technology.

We opened our first overseas office in June 2016 in Singapore. Located in Singapore Science Park I, the office cooperates with countries throughout the Asia-Pacific region. Since opening the office, Japan and Singapore began research collaborations in the field of "Biological and Molecular Determinants of Human Aging."

Then, in November the same year, we established our U.S. office. Based in Washington, D.C. – the home of the U.S. government – the office cooperates with countries throughout North and Latin America to strengthen ties. Its key roles

include building stronger connections with the medical research community in Japan.

Our London office is the newest of our overseas bases, opened in February 2017. It is responsible for cultivating relationships and promoting our work among our counterparts in Europe, the Middle East and Africa. The office is also heavily involved in the field of healthy aging, and last year hosted multiple symposiums on the topic.

Our overseas offices allow us to exchange information on research policies and best practices, and build stronger connections with the countries in each office's regions.

AMED's London Office, opened in February 2017, is the latest addition to our overseas bases



Professor Kenjiro Kosaki of Keio University introduces IRUD to Queen Letizia of Spain
Photo: Keio University Public Relations Office

A Royal Visit

In April 2017, we were honored to host Queen Letizia of Spain at Keio University's School of Medicine – one of AMED's core IRUD institutes.

The visit, which followed the signing of a Memorandum of Cooperation between AMED and Spain's State Secretariat for Research, Development and Innovation (SEIDI), began with a presentation by President Suematsu and introductions to various members of Keio University Hospital and the School of Medicine.

Queen Letizia then received an introduction to IRUD by Professor Kosaki at The Institute of

Integrated Medical Research. He explained the key role in which the School of Medicine plays in the research and development of genome analysis, and went into detail about the search for diagnoses of rare and undiagnosed diseases.

As a former journalist, the Queen displayed a high level of interest in the efforts of AMED. Like Japan, Spain is highly active in the fight against rare diseases, and during Queen Letizia's visit, she spoke of her desire for research to progress further due to the signing of the MOC between AMED and SEIDI.

GACD Joint Research Call

In November 2017, we collaborated with the Global Alliance for Chronic Diseases (GACD) – a joint international call on mental health for which two research projects were awarded grants.

It was a valuable experience to participate in an international joint peer review – the first such opportunity since our establishment in 2015. From the 1st-stage review in Tokyo to a panel meeting in Cape Town, South Africa, the whole process was conducted in English – another first for us.

Through participation in the program, we were given access to world-class research proposals and reviewers. This was an excellent opportunity to identify our own strengths and weakness, and gain a greater understanding of international collaborative research projects.

Going forward, as we look to work closer with our counterparts overseas, we will increase efforts to strengthen joint research calls and proposal reviews in English.



Members of the GACD joint peer review panel, including AMED-recommended reviewers, in Cape Town, South Africa
Photo: GACD

International Collaboration

Partnerships for Progress

As part of our strategic international activities, we have established formal partnerships with some of the world's leading funding agencies and government organizations.

To date, we have entered Memorandums of Cooperation with organizations in five countries: the National Institutes of Health (NIH), U.S.; the Agency for Science, Technology and Research (A*STAR), Singapore; the Medical Research Council (MRC), U.K.; the Ministry of Health, Lithuania; and Research, Development and Innovation (SEIDI), Spain.

Our relationship with A*STAR began in March 2016, and since then, we have undertaken three joint research projects in the field of “Biological and Molecular Determinants of Human Ageing” under the Strategic International Collaborative Research Program (SICORP).

Our partnership with SEIDI, announced in April 2017, marked the 150th anniversary of diplomatic relations between Spain and Japan. Our first research program together focuses on the field of nanomedicine, and is a joint effort between SICORP and SEIDI's State Programme for Research, Development and Innovation Oriented to the Societal Challenges of Spain (PEI+D+I)*.

We are also signatories of six international consortiums: the International Rare Diseases Research Consortium (IRDiRC), the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R), the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), the Global Alliance for Chronic Diseases (GACD), the Clinical Data Interchange Standards Consortium (CDISC), and the Global Alliance for Genomics and Health (GA4GH). By increasing our participation in international endeavors, we can collect information from around the world and contribute to international joint research.

Moving forward, we will continue to reinforce international relationships while utilizing each country's strengths through collaborative research and data sharing.

*Programa Estatal de Investigación, Desarrollo e Innovación Orientada a los Retos de la Sociedad (in Spanish).

Carmen Vela, Secretary of State of SEIDI, and Makoto Suematsu, President of AMED, signed a Memorandum of Cooperation in April 2017



As part of our global activities, we hosted the IRDiRC Assembly in November 2017

Asia's First IRDiRC Consortium Assembly

Since joining the International Rare Diseases Research Consortium (IRDiRC) in 2015, we have been closely involved in a range of core activities, and in November 2017, AMED hosted the 6th IRDiRC Consortium Assembly in Tokyo, Japan – the first of its kind in Asia.

AMED was honored to host the Consortium Assembly, which takes place twice a year and consists of public, private and corporate funders in rare diseases research, as well as umbrella organizations of patient advocacy groups. The timing of the Consortium Assembly provided the perfect opportunity to discuss new goals concerning rare diseases research for the next decade – an initiative known as “IRDiRC Goals 2017–2027.”

The first of two days featured a session entitled ‘Strengths and Challenges in Rare Diseases Research in Japan’ – an in-depth study of the traditional yet unique Japanese Nan-Byo research landscape. Members of Japan's Ministry of Health, Labour and Welfare and the Pharmaceuticals and Medical Devices Agency joined AMED speakers to present a wide range of topics, including policy, regulatory, funding and data-sharing issues.

Through discussion within IRDiRC, we will seek further data-sharing opportunities and ensure patients are given the best chance of receiving a diagnosis and treatment. Our strategic partnerships with like-minded people, organizations and institutes hold the key to improving society and the lives of everyone in it.

Other International Efforts

We are currently involved in a number of other overseas collaborative research programs, three of which are highlighted below:

1. UK-Japan Neuroscience Symposium

The first neuroscience symposium was held under the MOC between AMED and the Medical Research Council (UK). The two-day symposium, held in London in March 2018, featured research presentations and discussions into the field of healthy aging. It was an opportunity for new research partnerships and scientific collaborations to develop, and created a new platform between the UK and Japan.

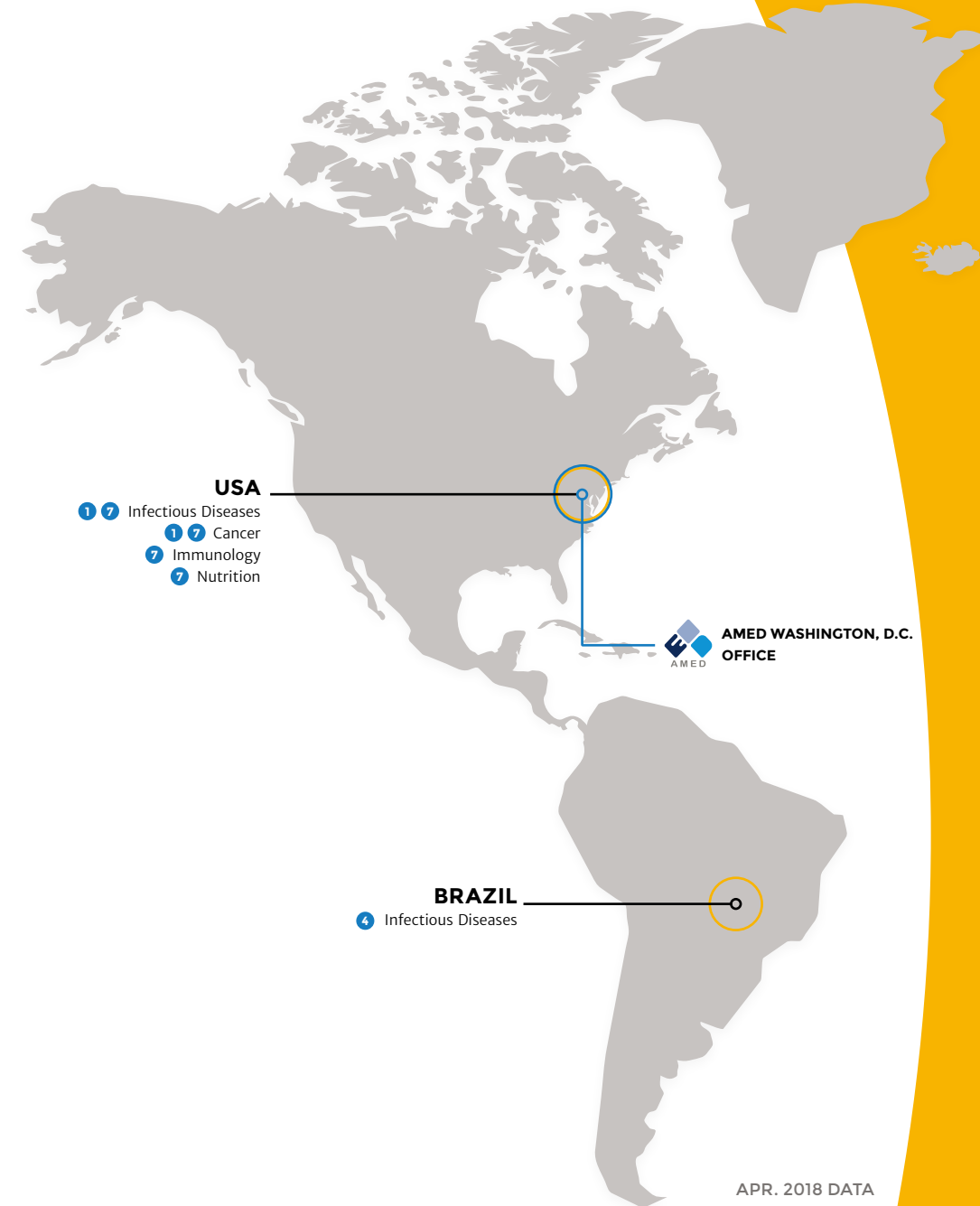
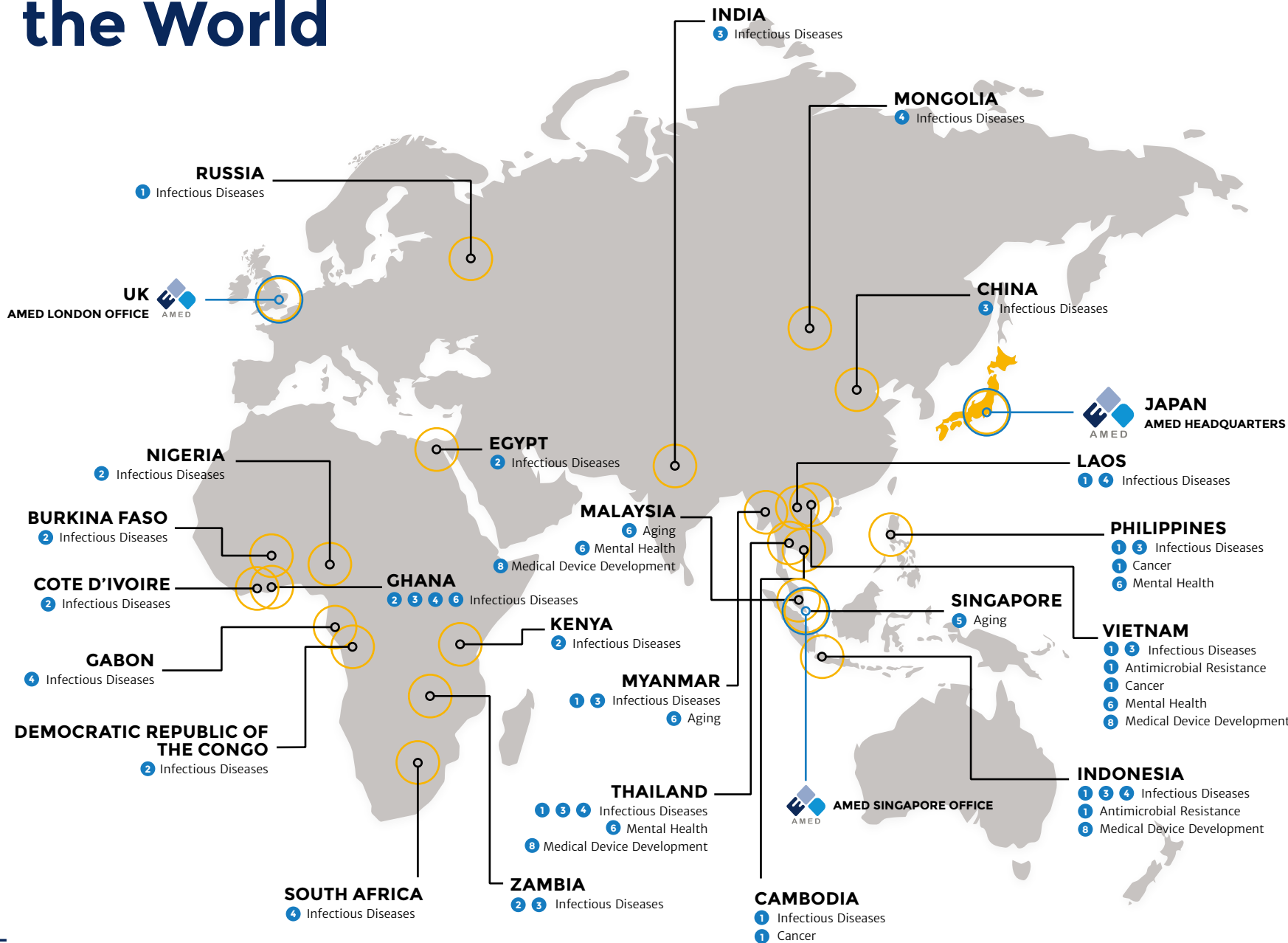
2. J-PRIDE Researchers Abroad

As part of the Japanese Initiative for Progress of Research on Infectious Disease for Global Epidemics (J-PRIDE), eight Japanese researchers visited the UK in December 2017 and held joint workshops at research institutes, such as the University of Glasgow, to develop concrete ideas for Japan-UK collaborative research projects. During the visit, researchers from both sides introduced their work, and discussions took place to identify possibilities for collaborative research and joint projects.

3. Health Technology for Developing and Emerging Countries

Developing and emerging countries face public health challenges that differ from those in Japan. Therefore, it is fundamental to identify individual needs firsthand by immersing oneself in local clinical sites. AMED's Research Program on Practical Application of Health Technology for Developing and Emerging Countries was established to support such intentions. Started in 2017, the program currently runs three research and development projects in Thailand, Vietnam, Malaysia, and Indonesia.

Our Work Around the World



With a global network of researchers, institutions and organizations across five continents, we recognize the importance of international presence and collaboration.

AMED is currently implementing 8 international cooperative research projects that tackle 52 issues across 23 countries.

- 1 e-ASIA JRP (e-ASIA Joint Research Program)
- 2 ICREP-NTDs (International Collaborative Research Program for Tackling the Neglected Tropical Diseases Challenges in African Countries)
- 3 J-GRID (Japan Initiative for Global Research Network on Infectious Diseases)
- 4 SATREPS (Science and Technology Research Partnership for Sustainable Development)
- 5 SICORP (Strategic International Collaborative Research Program)
- 6 Global Health (Research Program on the Challenges of Global Health Issues)
- 7 U.S.-Japan Cooperative Medical Sciences Program
- 8 Research Program on Practical Application of Health Technology for Developing and Emerging Countries

In addition, our overseas offices serve as hubs to support our global network.

Global Successes

Medical R&D has the potential to spare millions from suffering. We believe any outcome that makes life better is valuable – no matter how small.

The following pages contain snapshots of the work we are currently involved in to ensure safer, more effective healthcare around the world.

SCIENCE AND TECHNOLOGY RESEARCH PARTNERSHIP FOR SUSTAINABLE DEVELOPMENT PROGRAM (SATREPS)

Surveillance of Malaria and Other Parasitic Diseases in Laos

AMED is supporting the development of innovative research techniques for the control of parasitic diseases in Laos. The study, in collaboration with the Japan International Cooperation Agency (JICA), is one of nine that AMED is currently conducting in the field of infectious disease control in developing countries as part of SATREPS.

Dr. Shigeyuki Kano (National Center for Global Health and Medicine) and his study group – in close collaboration with researchers from the Institut Pasteur du Laos, Center of Malariology, Parasitology and Entomology, etc. – are studying the molecular genetic epidemiology of malaria and other parasitic infectious diseases. The aim of which is to control epidemic spread and disease based on scientific knowledge.

The study involves monitoring endemicity and developing new diagnostic methods for malaria and other parasitic diseases, such as opisthorchiasis and schistosomiasis. In addition, the team is working to elucidate emergence mechanisms and prevent the expansion of drug-resistant malaria. Scientific evidence obtained in the study is utilized to assist health services in the control of parasitic disease in Laos.

The study has already produced a number of outcomes. Dr. Kano and his team developed new gene diagnostic methods (LAMP, etc.) for various parasitic

diseases, and a highly sensitive diagnostic method (ELISA) for schistosomiasis. Many cases of drug (artemisinin) resistant malaria were discovered in the southern provinces of Laos – those most impacted by the endemic. It was also found that the resistant malaria was spreading north. Also, by using the gene diagnostic method, the team discovered that there were many asymptomatic malaria parasite carriers, most of which could not be detected using standard methods (microscopy and rapid diagnostic test kits).

The team is currently monitoring and analyzing endemicity in detail, and working to validate the developed diagnostic methods. Going forward, they will make policy recommendations on parasitic disease control to the Ministry of Health in Laos.



Concept

Support studies to monitor genetic endemicity and develop new diagnostic methods for malaria and other parasitic diseases. Elucidate emergence mechanisms and the expansion of drug-resistant malaria. Contribute to parasitic disease control in Laos.



Progress

New rapid gene diagnostic methods have been developed for parasitic diseases. The epidemic status of drug resistant malaria is closely monitored in endemic areas, while spreading patterns are constantly analyzed. The newly developed gene diagnostic method led to the discovery of asymptomatic malaria parasite carriers – most of which could not be detected using standard methods of diagnoses.



Collaborators

National Center for Global Health and Medicine (NCGM); Institut Pasteur du Laos (IPL); Center of Malariology, Parasitology and Entomology (CMPE); National Institute of Public Health (NIOPH); Other Departments of the Ministry of Health, Laos PDR

INTERNATIONAL COLLABORATIVE RESEARCH PROGRAM FOR TACKLING THE NEGLECTED TROPICAL DISEASES (NTDS) CHALLENGES IN AFRICAN COUNTRIES

Integrated Research for the Control of Dengue Fever in Burkina Faso

Neglected Tropical Diseases (NTDs) are prevalent in 149 countries around the world, and the number of NTD patients has already exceeded 1.4 billion. Almost half of these patients reside in Africa, where NTDs are particularly rampant.

The International Collaborative Research Program for Tackling the Neglected Tropical Diseases Challenges in African Countries (ICREP-NTDs) was established in 2015 to enable cooperation between research institutions in Japan and Africa. The program facilitates international joint research projects, human resource development and international standardization. The overall goal of which is to control NTDs and create a safer Africa.



One aspect of the large-scale initiative was the Integrated Research Program for the Control of Dengue Fever in Burkina Faso, which began in November 2015. A collaboration between the Jikei School of Medicine in Japan and Université Ouaga in Burkina Faso, the program was a study into the distribution of dengue fever through mosquitos – the first study of its kind in recent years.

It was clear that a new, short-term strategy was necessary until a successful vaccine or long-term control method was discovered. In response, a study into the diagnosis, ethology, immunity, and epidemiology of vector species was performed and an Integrated Vector Management (IVM) system was developed to control the mosquitos and the spread of dengue fever.

As part of the IVM system, a single-step RT-LAMP assay was developed to detect not only Dengue fever, but also the Zika virus in mosquitos. Furthermore, a biocontrol strategy that uses an obligate intracellular bacterium to limit the replication of Dengue in mosquitos is currently under development.

Following the two-year program, a new detection technology – the vDNA-LAMP method – was also introduced in September 2017. The simple device enables local scientists and researchers to easily perform virus inspections on mosquitos, and will ultimately assist in the fight against NTDs in Africa.



Concept

Utilize Japan's scientific and technological capabilities to contribute towards the fight against Neglected Tropical Diseases (NTDs) in Africa, including Dengue fever in Burkina Faso. Assist emerging and developing African nations by strengthening scientific, technological and human resource ties.



Progress

Research from the international collaborative research program has resulted in two new methods of virus detection, while a biocontrol strategy against Dengue fever in Burkina Faso is currently under development.



Collaborators

Jikei University School of Medicine, Japan; Université Ouaga, Burkina Faso

THE INTERSTELLAR INITIATIVE

Aligning the Young Stars of Science

The Interstellar Initiative recognizes the world's most promising Early Career Investigators (ECIs) and connects them with peers in related yet distinct disciplines. The initiative, introduced by AMED in partnership with the New York Academy of Sciences in 2018, provides a platform to develop solutions to major medical research questions.

Following an international open call for participants, ECIs are selected from a wide range of disciplines and grouped into teams of three,

including one Japanese member. Together, they devise research proposals for submission to international funding agencies.

Participants are invited to two workshops, where they work closely within their teams to develop and refine proposals. With participants from such a wide variety of backgrounds including medical biology, natural science and technology, the workshops provide ECIs the opportunity to learn outside of their chosen field. For some, it is also their first opportunity to collaborate with overseas peers.

During the workshops, each team also receives guidance and advice from experienced mentors. The mentors, who belong to global research institutions, assist the ECIs and inspect the feasibility of their proposals ahead of submission to funding agencies.

Once funding for a study is acquired, the international collaborative investigation begins, and is led by the same three-person ECI team that created the initial proposal.

By establishing such an initiative, AMED aims to accelerate the globalization of medical research and development from Japan, and help to plant new seeds for medical innovation by nurturing promising young researchers and scientists.

The initiative is also part of a broader strategy to bring international partnerships and new funding streams to Japan's efforts to realize the world's most advanced medical care.



19 Photo courtesy of the New York Academy of Sciences. Photographer: Matt Carr



Concept

Connect Early Career Investigators from Japan with their peers from around the world. Build a network to encourage interdisciplinary research and development, and plant new seeds to accelerate the pursuit of medical innovation through global collaboration.



Progress

This initiative started in 2018, and the targeted research fields are set to change every year. In 2018, neuroscience and cancer are the primary focus of the Interstellar Initiative. Artificial Intelligence (AI) has also been designated as a key area of research. The Early Career Investigators — who will participate in two workshops that will be held on June 22 – 23, 2018, and January 31 – February 1, 2019 — will be recruited from a wide range of research areas, including not only biomedicine, but also physical science and technology.

In 2017, a feasibility study of the Interstellar Initiative was held, which focused on cancer, neuroscience, and regenerative medicine. The feasibility study was jointly conducted by AMED and the New York Academy of Sciences. An article describing the feasibility study can be found at: <https://www.nyas.org/AMEDInterstellar>

THE JAPAN INITIATIVE FOR GLOBAL RESEARCH NETWORK ON INFECTIOUS DISEASES (J-GRID)

The Association Between Zika and Microcephaly in Vietnam

In response to the worldwide threat posed by potential pandemic infectious diseases in Asia and Africa, AMED has been supporting J-GRID since 2015. The program encourages relationships with its nine collaborative research centers throughout Asia and Africa to promote the epidemiological research of infectious disease pathogens and explore new diagnostic systems, therapeutics and vaccines. Influenza, antimicrobial resistant strains, infectious diarrheal diseases and dengue fever are the current priority subjects of J-GRID, with studies taking place in areas directly affected by infectious diseases.

One such study, conducted by Dr. Hasebe and his team (Nagasaki University) in collaboration with the World Health Organization and National Institute of Hygiene and Epidemiology (NIHE), provided medical evidence to prove the link between the Zika virus and microcephaly in Vietnam.

Vietnam's first case of Zika was discovered in March 2016 by Nagasaki University and the NIHE in Hanoi, when a Zika virus gene was detected in a test specimen and confirmed via sequence analysis.

However, due to the similarities between Zika and dengue fever, it was difficult to distinguish between the two viruses by using existing diagnostic methods. In response, two new tests were introduced by Nagasaki University: an in-house IgM ELISA assay and plaque reduction neutralization test (PRNT). The tests assisted in the discovery and confirmation of Zika cases in Vietnam — a total of 223 cases in less than one year.

In November 2016, researchers gathered serum from a newborn baby with microcephaly in the Dak Lak Province. Testing of the child, her immediate family and neighbors revealed high titers of Zika virus-specific neutralizing antibody, confirming recent viral exposure. An association between microcephaly and the Zika virus was then confirmed.

The study was the first of its kind in Asia to identify the risks of congenital Zika virus syndrome, proving the association of microcephaly with the disease through diagnostic data and highlighting the need for further investigation.

While its spectrum remains undefined, Dr. Hasebe and his team will strive to gain a better understanding of the virus and the infection prophylaxis in pregnant women throughout Asia.



Concept

Utilize the plaque reduction neutralization test (PRNT) for the identification of the Zika virus infection in Vietnam. Discover Zika-associated microcephaly via PRNT.



Progress

In March 2016, Vietnam's first case of Zika was identified, and in August of the same year, the NIHE introduced PRNT to distinguish between dengue and Zika virus infection. Following its introduction, the first case of Zika virus associated microcephaly was detected in Vietnam.



Collaborators

Nagasaki University; National Institute of Hygiene and Epidemiology (Vietnam); The World Health Organization

REGENERATIVE MEDICINE

The World's First Allogeneic iPSC-derived Retina Cell Transplant

Seeking to become a global leader in the field of stem cell technology, AMED is supporting research and development towards the clinical application of regenerative medicine based on stem cell technology.

In 2014, Masayo Takahashi, Project Leader of the RIKEN Center for Developmental Biology began the world's first clinical study of induced pluripotent stem cells (iPSCs), using iPSC-derived retinal pigment epithelial (RPE) cell transplantation to treat age-related macular degeneration (AMD).

AMD is a relatively common eye condition among people over 50 that causes damage to the macular – a small spot on the center of the retina essential for clear vision. Dr. Takahashi and her team first succeeded in treating the disease in 2014, in a procedure involving reprogrammed iPSCs from the patient's own RPE cells.

Although the procedure was a remarkable breakthrough in regenerative medicine, certain obstacles remain due to the high expenses and excess cultivation time related to using iPSCs from the patient's own RPE cells.

To overcome such hurdles and introduce the use of allogeneic iPSCs, Kyoto University's Center for iPS Cell Research and Application (CiRA) developed medical iPSC stock with cells collected from extremely rare donors – those with Human Leukocyte Antigens with low immunorejection. This ensures iPSCs can be rapidly accessed when necessary.

This process led to another world's first, when in March 2017, an allogeneic RPE transplant was successfully carried out at the Kobe City Medical Center in collaboration with Osaka University. By November of the same year, a further five patients had received transplants using allogeneic iPSCs.

As it stands, stock iPSCs match approximately 32% of the Japanese population, but CiRA aims to increase this figure to 50% by 2022.

Moving forward, as expectation surrounding regenerative medicine increases, AMED aims to lead the way in the research, development and application of allogeneic iPSC-based regenerative medicine, keeping safety and efficacy at the heart of everything we do.



Photo courtesy of the Kobe City Medical Center General Hospital.



Concept

Examine the safety of RPE cell transplantation. Utilize allogeneic iPSCs to develop new treatments for AMD. Contribute to enhancing the lives of patients through regenerative medicine.



Progress

Since the first successful generation of iPSCs by Professor Shinya Yamanaka in 2007, regenerative medicine has progressed significantly. 2014 saw the world's first transplant operation of RPE cells from a patient's own iPSCs, and in March 2017, allogeneic iPSCs were first used in procedure. To date, five patients have undergone successful transplants.



Collaborators

RIKEN Center for Developmental Biology; Center for iPS Cell Research and Application, Kyoto University; Foundation for Biomedical Research and Innovation at Kobe, Kobe City Medical Center General Hospital; Graduate school of Medicine, Osaka University

INITIATIVE ON RARE AND UNDIAGNOSED DISEASES (IRUD)

Ending a Diagnostic Odyssey: Going Beyond the Identification of Unidentified Conditions

Japan has a long history of tackling rare and intractable diseases (known locally as Nan-Byo). Building on this heritage, AMED – in collaboration with researchers and the Japanese universal healthcare system – launched the Initiative on Rare and Undiagnosed Diseases (IRUD) in 2015.

The initiative has led to the construction of a nationwide medical research consortium dedicated to helping patients receive diagnoses. The network enables primary healthcare clinics to collaborate with general hospitals and IRUD Clinical Centers, where multi-disciplinary IRUD Diagnosis Committees can review complex cases. This process is supported by five IRUD Analysis Centers throughout Japan, which administer genetic tests and share findings with the committees.

The clinical and genetic data is stored in a globally compatible patient-matching system and shared with domestic and overseas medical organizations in compliance with existing rules.

As a result, similar cases can be compared with a broader pool of patients around the world, increasing the chances of successful definitive diagnoses. Thanks to the progress of IRUD's international data sharing, new rare diseases were identified in Canada and Lithuania – two of many countries where disease discovery through patient matching had yet to come.

As IRUD's pioneering efforts continue to grow, so too do our next steps. "IRUD Beyond" consists of three AMED-supported pillars designed to build on

IRUD research:

- 1. Beyond Diagnosis: The invention of innovative medical drug candidates by targeting mutations discovered in IRUD research.
- 2. Beyond Genotyping: Functional genomics studies and further attempts to address cases that remain unsolved even after next-generation sequencing analysis.
- 3. Beyond Borders: Enhanced international data sharing via globally compatible systems.

In addition, working to fulfill AMED's foundational role of global harmonization through valuable forums such as the International Rare Diseases Research Consortium (IRDiRC), IRUD will seek further data-sharing opportunities and ensure patients are given the best chance of receiving a definitive diagnosis.



Concept

Construct a comprehensive medical network, establish valuable clinical databases and facilitate data sharing to propel the study of rare and undiagnosed diseases.



Progress

IRUD has grown into a collaborative nationwide network of primary healthcare clinics, over 400 general hospitals, 37 IRUD Clinical Centers, a Data Center and 5 Analysis Centers as of April 2018. In addition, a globally compatible patient-matching system has been established to store and share clinical and genetic data. In 2017 alone, almost 800 diagnoses were made, while 9 new diseases were discovered.



Collaborators

National Center of Neurology and Psychiatry; National Center for Child Health and Development; Keio University; Yokohama City University; hundreds of related institutions and responsible individuals

ORGANIZED REGISTRATION FOR THE ASSESSMENT OF DEMENTIA ON NATIONWIDE GENERAL CONSORTIUM TOWARD EFFECTIVE TREATMENT IN JAPAN (ORANGE REGISTRY)

Overcoming Dementia in Super-Aging Society

Japan, more than most countries, faces sharp increases in the proportion of its population aged 65 years and over. With that, the number of dementia sufferers is expected to increase even further, with 9 million cases predicted by 2040. Despite such a serious situation, progress in the development of preventative dementia medicine has slowed in the past 10 years.

In response, AMED developed the Orange Registry in 2016, with Dr. Kenji Toba (President of The National Center for Geriatrics and Gerontology) as Principal Investigator. From the outset, we began to collect information from people with preclinical, mild cognitive impairment (MCI), slight, moderate and advanced dementia – as well as those without the disease – in order to clarify therapeutic methods and care techniques.

The nationwide registration and coordination system caters to the long-term follow-up period associated with dementia research and encourages novel ideas.

It also assists in the clinical observation of dementia sufferers at each stage of their journey, from preclinical to dementia care.

Research shows that 21% of senior citizens, who at first appear healthy, are already at the MCI stage of dementia. During the early stages of MCI, recovery is possible, so careful observation and access to drug trials is an essential part of the Orange Registry.

At the pre-clinical stage, community-dwelling cohorts are urged to participate in dementia-related studies. Registrants of IROOP™ (Integrated Registry of Orange Plan) – an internet-based dementia study – answer simple questionnaires and undergo cognitive functionality checkups. Data gathered at this stage is used toward the study of pre-emptive medicine and lifestyle interventions.

Furthermore, AMED promotes best practices for dementia care and supports the research and development of innovative new technologies. As part of the Orange Plan, a partner robot and an unmanned care robot will be newly developed. Other recent activities include a study into the causation of hearing loss and dementia, and the development of an application for Behavioral and Psychological Symptoms of Dementia in care facilities.

At present, there is no simple, non-invasive method of diagnosing dementia, while therapeutic and prophylactic treatments have yet to become standardized. Through the Orange Registry, AMED aims to be the first to develop new diagnosis methods, treatments, medication and care techniques to assist Japan's super-aging society.



Concept

Establish a nationwide registry and coordination system for the clinical observation of dementia sufferers. Focus on each stage of dementia – from preclinical to mild cognitive impairment (MCI) and dementia care. Develop new treatments, medications and care techniques by utilizing the accumulated data.



Progress

1,156 dementia sufferers and 32 dementia-related institutions have joined the Orange Registry (2016).



Collaborators

National Center of Neurology & Psychiatry, Tokyo Dementia Care Research and Training Center (care technology); Tokyo Metropolitan Geriatric Hospital and Institute of Gerontology (Itabashi cohort); National Center for Geriatrics and Gerontology, The Center for Comprehensive Care and Research on Memory Disorders (Obu cohort)

ACCELERATION TRANSFORMATIVE RESEARCH FOR MEDICAL INNOVATION (ACT-M)

Safer, More Accurate Surgery: The Development of a New Medical Imaging Projection System

At AMED, we strive to promote innovative technologies that respond to current, pressing medical needs, and in FY2015, we initiated ACT-M: Acceleration Transformative Research for Medical Innovation.

An industry-academia collaboration, ACT-M encourages open innovation and venture development in a range of fields, including the development of medicine, medical treatment and medical equipment.

As part of the program, our research led to the development of a new type of medical equipment: a Medical Imaging Projection System (MIPS). The real-time navigation system – a world's first – combines near-infrared fluorescence-guided surgery with projection mapping technology to significantly enhance the safety and accuracy of hepatectomy procedures.

While near-infrared fluorescence color systems are useful, existing methods require a handheld camera and monitor. This means surgeons must frequently shift their view from the patient's organs to the monitor to confirm fluorescent images, while surgical lamps must regularly be switched on and off to avoid complications.

The utilization of projection mapping helps to overcome such problems, and allows surgeons to fully focus on the patient's organs. It eliminates the need for display monitors, and projects accurate guidelines directly onto the operating field. As a result, accuracy greatly improves while the surgeon carries less of a burden.

A clinical study conducted at Kyoto University Hospital compared hepatectomy on patients with and without the use of MIPS. Results showed the use of MIPS had a tendency to increase the accuracy of dissections. In addition, MIPS showed high sentinel lymph node identification rates in breast cancer surgery, confirming the effectiveness of real-time navigation.

Moving forward, we will continue to develop MIPS in order to enhance its capabilities and increase the accuracy of surgery. This way, we aim to further reduce the burden on surgeons and ease the postoperative recovery of patients.

*MIPS projecting onto an artificial liver.
The lesion to be surgically removed is highlighted.*



Concept

The development of a new Medical Imaging Projection System (MIPS) with near-infrared fluorescence, for use in real-time navigation surgery. For safer, more accurate hepatectomy procedures.



Progress

Since introducing our first-generation equipment with a class-one pharmaceutical approval rating in FY2015, we have come a long way on our journey for medical innovation. In FY2016, we recognized the advantages of MIPS from the results of a clinical study, and in FY2017, we made further enhancements to the equipment and began developing second-generation equipment. In FY2018, we plan to apply for a class-two pharmaceutical approval rating.



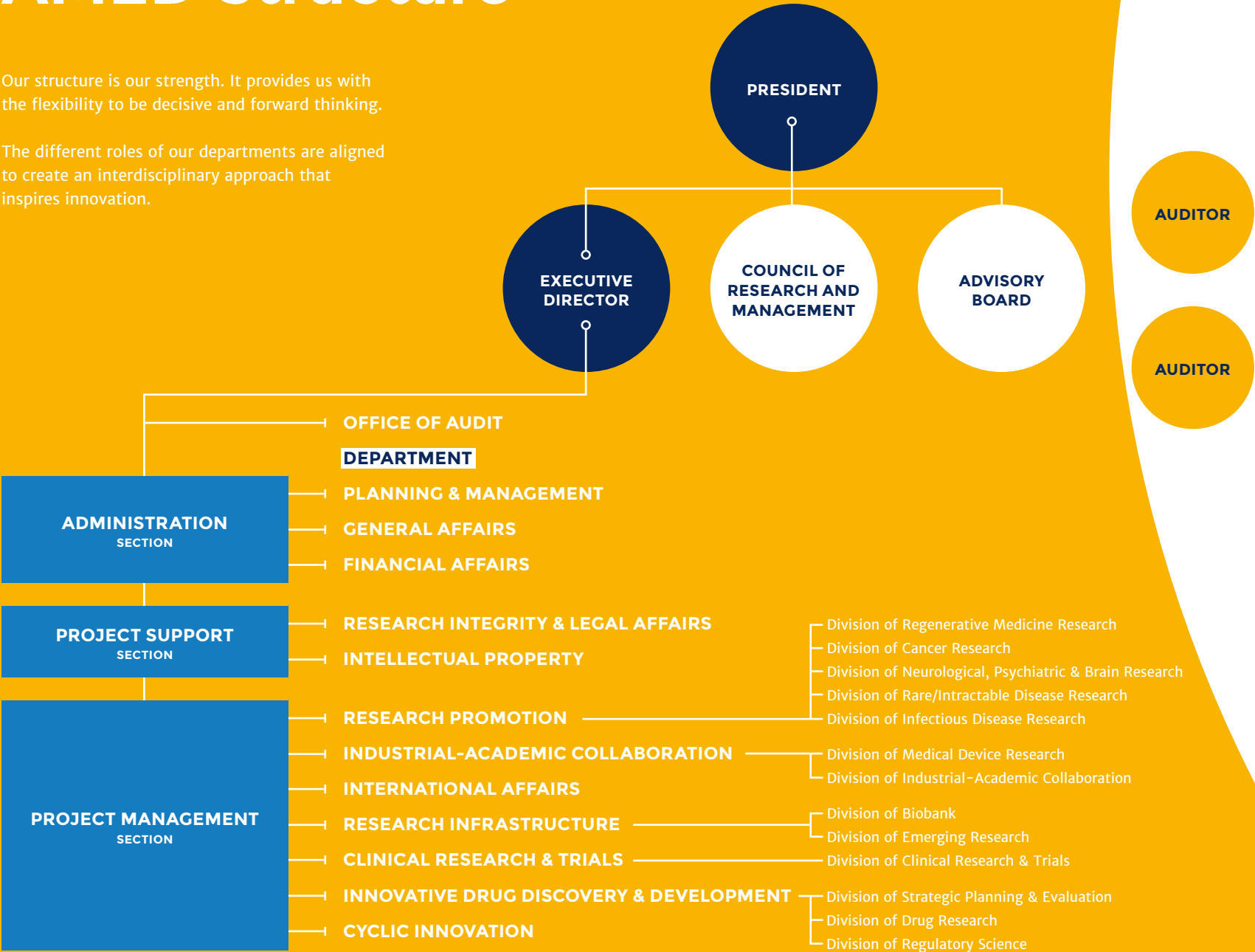
Collaborators

Panasonic Corporation; Kyoto University Hospital; MITAKA KOHKI CO., LTD.

AMED Structure

Our structure is our strength. It provides us with the flexibility to be decisive and forward thinking.

The different roles of our departments are aligned to create an interdisciplinary approach that inspires innovation.



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