Current Situation Regarding Infections Caused by Bacteria, with Antimicrobial Resistance (AMR) and KS-Project together with the Kitasato Institute Covered by the Cyclic Innovation for Clinical Empowerment (CiCLE)

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The emergence and spread of antimicrobial drug-resistant bacteria has become a global problem. Thus, urgent measures are being called for both at national and international levels. The Kitasato Institute and Sumitomo Dainippon Pharma Co., Ltd. are aiming to provide groundbreaking anti-infective drugs through unprecedented and original approaches, under the KS-Project joint drug discovery research. This paper describes the global problem of antimicrobial drug-resistant bacteria and our antimicrobial drug discovery project covered by the CiCLE.

This paper is translated from R&D Report, "SUMITOMO KAGAKU", vol. 2019.

Introduction

Many antimicrobial drugs that are essential for the treatment of bacterial infections were developed in the 20th century, and humans appeared to have overcome most bacterial infections. However, since the beginning of the 21st century, the emergence and increase of bacteria with antimicrobial resistance (AMR) to many of these antimicrobial drugs have become global problems. The spread of antimicrobial drug-resistant bacteria indicates a return to the days when our lives were at risk because of not only common infections, such as pneumonia, but also infections that occur after simple surgery. Furthermore, O'Neill predicted that neglecting to take measures for AMR would result in 10 million annual deaths from infections caused by antimicrobial drug-resistant bacteria in 2050, which exceed deaths from cancer, and corresponds to an economic loss of 100 trillion US dollars.[1)]

Although the development of antimicrobial drugs that are effective against antimicrobial drug-resistant bacteria has become a globally urgent issue, many pharmaceutical companies have withdrawn from the field of bacterial infections in recent years, and the development pipeline for conventional antimicrobial drugs has been quite lacking. The lack of advancement in this field is due to the low profitability of antimicrobial drugs, difficulties in conducting clinical studies of drugs for the treatment of infections caused by drug-resistant bacteria, and the difficulty of searching for "seeds" of drug discovery. The number of new antimicrobial drugs launched in Japan peaked between 1976 and 1985 and has since decreased annually[2)] (**Fig. 1**).

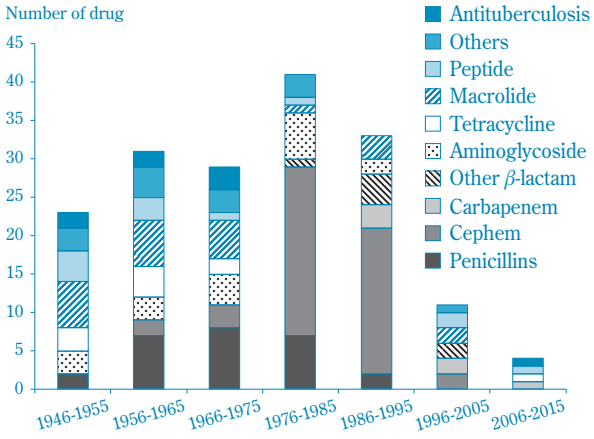

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Fig. 1 New antibacterial agents launched in Japan

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New β-lactam antimicrobials that are effective against a wide range of bacterial species have rapidly decreased since 1995, and no new macrolide or cephem antimicrobials were launched between 2006 and 2015. The situation is similar in the United States[3]; the development of new drugs has stagnated in the field of bacterial infections, and actions against antimicrobial drug-resistant bacteria are facing a critical situation.

This paper describes the research and development of antimicrobial drugs in our company; provides background information on antimicrobial drug-resistant bacteria and an outline of the mechanism of resistance; discusses global trends, issues, and measures for promoting the discovery of new antimicrobial drugs; and lastly, highlights research on the discovery of drugs for the treatment of infections caused by antimicrobial drug-resistant bacteria that is conducted by the External Innovation of our company, that is, the "KS-Project" (Kitasato-Sumitomo Dainippon Antimicrobial Resistance [AMR] Drug Discovery Project), which is a 10-year joint research project with the Kitasato Institute and covered by the Cyclic Innovation for Clinical Empowerment (CiCLE) of the Japan Agency for Medical Research and Development (AMED).

Development of Antimicrobial Drugs at Sumitomo Dainippon Pharma Co., Ltd.

Our company has conducted in-house research and development and has launched the following drugs for the treatment of infections: quinolone antimicrobials (oral formulations) including enoxacin (brand name Flumark, launched in 1985), sparfloxacin (brand name Spara, launched in 1993), and gatifloxacin (brand name Gatiflo, launched in 2002); and new β-lactam antimicrobials (injections) including apalcillin (brand name Lumota, launched in West Germany in 1983), cefpiramide (brand name Sepatren, launched in 1985), and meropenem (brand name Meropen, launched in 1995). Furthermore, after the discovery of meropenem, our company conducted research and development on an anti-MRSA (methicillin-resistant *Staphylococcus aureus*) carbapenem (SMP-601) and on oral carbapenem, which has led to joint research with other companies or out-licensing. Although our company temporarily discontinued research activities for new drugs after that, the company has continued the development of in-licensed products in Japan that had already been approved in foreign countries, including liposomal amphotericin B and ceftaroline, and has conducted supportive research on launched products (**Fig. 2**). However, because the global problems of antimicrobial drug-resistant bacteria and the need for drugs against these bacteria have been increasing, we believed several years ago that, despite significant difficulty, we should restart in-house research on drugs with new mechanisms for the treatment of infections caused by antimicrobial drug-resistant bacteria and have since been taking action. As mentioned above, we had the proper background for this undertaking: our company had research and development abilities and know-how that led to the launch of eight antimicrobial drugs including meropenem, which can accurately be described as the strongest antimicrobial drug by efficacy and safety and should be considered a human common asset, and we can still utilize the ability and know-how despite a temporary pending. Furthermore, although the meropenem patent has expired and generic versions of this drug are selling, the company still sells at least 20 billion yen in Japan and China because of its brand power, and new drugs in the field can expect to enhance company's pipeline. Above all, we thought that our company had

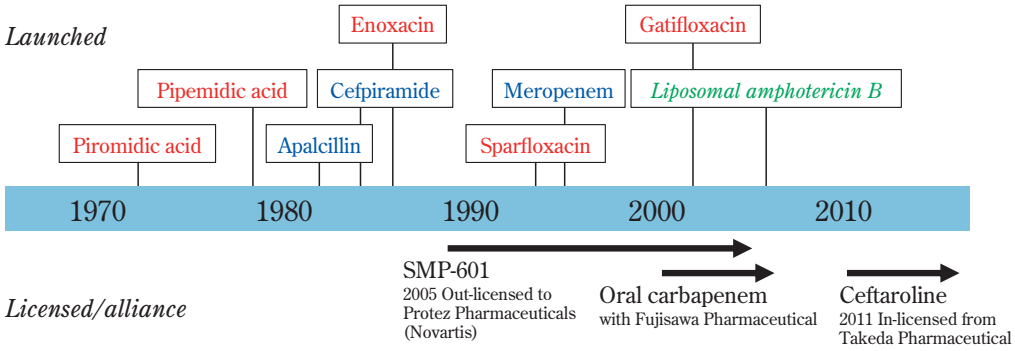

Fig. 2 History of antimicrobials developed by Sumitomo Dainippon Pharma Co., Ltd.
Blue: β-Lactams, Red: Quinolone, Green: Others

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the social responsibility to develop new drugs for the treatment of infections caused by antimicrobial drug-resistant bacteria.

Antimicrobial Drug-Resistant Bacteria

1. Emergence and Spread of Antimicrobial Drug-Resistant Bacteria

Because bacteria rapidly divide, mutations (errors) in genes are more likely to occur in bacterial cells than in animal cells; for example, bacteria obtain resistance by making changes in the target proteins on which antimicrobial drugs act. Moreover, they can transmit genetic factors between strains using transmissible plasmids, transposons, and bacteriophages, and obtaining external drug-resistant factors allows the bacteria to obtain a mechanism of resistance that cannot be obtained through gene mutations alone. Although antimicrobial drug-resistant bacteria have obtained resistance, their growth rate often decreases because of protein defects that contribute to their effective proliferation and the production of many proteins unnecessary for their survival; consequently, they are weak members of the bacterial flora in the struggle for existence and thus will normally die out naturally. However, adding antimicrobial drugs to the environment kills drug-sensitive bacteria, resulting in the survival of the antimicrobial drug-resistant bacteria, which used to be the weaker strains (antibiotic selective pressure) (**Fig. 3**).

Drug-resistant bacteria often die out when exposed to antimicrobial drugs at a higher concentration than that which kills drug-sensitive bacteria. However, a drug concentration between that which can inhibit the growth of drug-sensitive bacteria and that which can inhibit the emergence or growth of drug-resistant bacteria is called the mutant selective window, which theoretically is an environment where drug-resistant bacteria develop and proliferate most easily. Preventing underdosing of antimicrobial drugs is important to avoid exposing pathogenic bacteria to this window for a long time, and the antimicrobial stewardship is also important, including treatment with a sufficient dose of antimicrobial drugs that are the most suitable to the pathogenic bacteria causing the infection.

2. Mechanisms of Acquired Antimicrobial Resistance

The major mechanisms of acquired antimicrobial resistance include the following: [1] degrading or modifying antimicrobial drugs (inactivation), [2] mutations in antimicrobial drugs targets (modification), and [3] decreasing the concentration of antimicrobial drugs in the bacteria (pumping out and impermeability) (**Fig. 4**). Typical enzymes that degrade antimicrobial drugs to inactive them include β-lactamase, whereas enzymes that modify antimicrobial drugs to inactivate them include aminoglycoside-modifying enzymes (acetyltransferases, adenylation enzymes, and kinases). Mutation in targets to be acted on include: methylation of ribosomes, which are targets of macrolide antimicrobials; mutations in the 23S rRNA domain V of 50S ribosomes; and mutations in DNA gyrases or topoisomerase IV, which are targets of quinolone antimicrobials. Mechanisms of resistance that decrease the concentration of antimicrobial drugs in bacteria include the inhibition of influx because of the reduction or defect of porins (which play a role in nutrient intake in the outer membrane proteins); such porins are responsible for the permeability of antimicrobial drugs

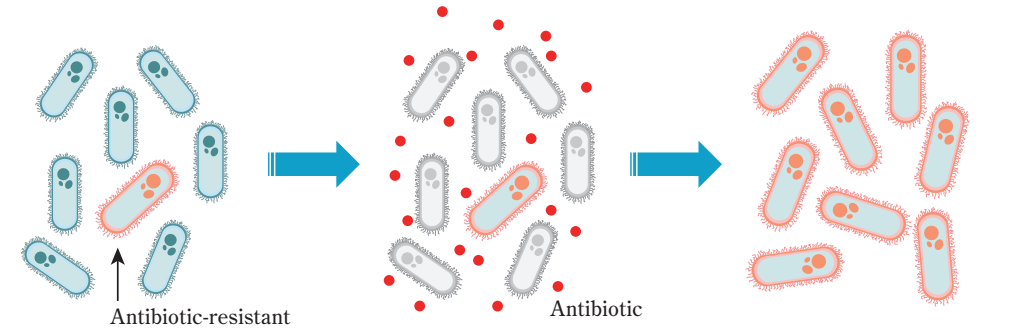

Fig. 3 Effect of selective antibiotic pressure in bacteria

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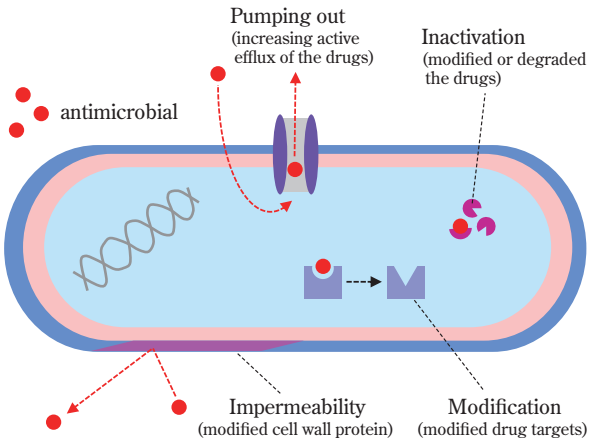

Fig. 4 Mechanisms of antimicrobial resistance

and can overexpress drug efflux pumps, thus facilitate transporting the drugs out of the bacteria.

Obtaining more than one mechanism of resistance to antimicrobial drugs in the same category causes high-level resistance whereas obtaining mechanisms of resistance to more than one antimicrobial drug causes multidrug resistance; these situations cause difficulties with treatment in clinical settings.

3. Antimicrobial Drug-Resistant Bacteria that Urgently Require the Development of New Antimicrobial Drugs

On February 27, 2017, the World Health Organization (WHO) announced 12 antimicrobial drug-resistant bacteria that were highly likely to threaten human health from a public health perspective and for which the development of new antimicrobial drugs was urgently required. These 12 pathogens were identified from a list of antimicrobial drug-resistant bacteria against which antimicrobial drugs generally used in the clinical setting were no longer effective[4] (**Table 1**). This was the first time that the WHO has announced such a list.

The category of "critical", which indicates the most urgent, includes three bacteria: carbapenem-resistant *Enterobacteriaceae*, which was named a "nightmare superbug" by the Centers for Disease Control and Prevention (CDC); carbapenem-resistant *Acinetobacter baumannii*; and carbapenem-resistant *Pseudomonas aeruginosa*. Carbapenems, including meropenem, are drug of last resort in the treatment of bacterial infections because they display a broad antimicrobial spectrum covering gram-positive bacteria, gram-negative bacteria, and anaerobic bacteria; thus, resistance to carbapenem is a serious problem. Simultaneously, because these drug-resistant bacteria are often resistant to other antimicrobials (multidrug resistance), difficult cases to treat occur one after another.

The major factors of resistant to carbapenem include inactivation in which β-lactamase (carbapenemase) hydrolyzes carbapenems; carbapenemases owned by *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacteriaceae,* that are categorized as "critical" in the WHO's list, degrade most β-lactams, such as carbapenems (**Table 2**).

Table 1 WHO Priority pathogens list

Priority 1: CRITICAL	
Acinetobacter baumannii	carbapenem-resistant
Pseudomonas aeruginosa	carbapenem-resistant
Enterobacteriaceae	carbapenem-resistant 3rd generation cephalosporin-resistant
Priority 2: HIGH	
Enterococcus faecium	vancomycin-resistant
Staphylococcus aureus	methicillin-resistant vancomycin intermediate and resistant
Helicobacter pylori	clarithromycin-resistant
Campylobacter	fluoroquinolone-resistant
Salmonella spp.	fluoroquinolone-resistant
Neisseria gonorrhoeae	3rd generation cephalosporin-resistant fluoroquinolone-resistant
Priority 3: MEDIUM	
Streptococcus pneumoniae	penicillin-non-susceptible
Haemophilus influenzae	ampicillin-resistant
Shigella spp.	fluoroquinolone-resistant

Table 2 β-Lactamase classification

Class	Typical enzyme	Active center	Substrate specificity
A	KPC, ESBLs	Serine	Penicillins (→ cephalosporines, carbapenems)
C	AmpC, CMY	Serine	Cephalosporins (→ penicillins, carbapenems)
D	OXAs	Serine	Oxacillins (→ penicillins, carbapenems)
B	NDM, VIM, IMP	Metallo (Zn)	All β-lactams (except monobactams)

Red: Carbapenemases

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Environmental Changes Related to the Development of Drugs for the Treatment of Infections Caused by Antimicrobial Drug-Resistant Bacteria

1. World Movement

In 2015, the WHO announced the "Global Action Plan on Antimicrobial Resistance",[5] which includes "increase investment in new medicines". To meet the WHO's demand, Japan established the Ministerial Meeting on Measures on Emerging Infectious Diseases in 2015 and announced the "National Action Plan on Antimicrobial Resistance" in April 2016; likewise, the "G7 Ise-Shima Leaders' Declaration" announced in the G7 Ise-Shima Summit in May 2016 a plan that included the "promote research and development of novel methods for treatment".

The Infectious Diseases Society of America issued messages of "Bad bugs, No Drugs" and "The 10 × '20 Initiative" in 2004 and 2010, respectively, and actively lobbied Congress, with a policy including the development of 10 antimicrobial drugs that are effective against antimicrobial drug-resistant bacteria by 2020.[6] These efforts resulted in an improved review system in a regulatory authority, the Food and Drug Administration (FDA), on drugs for the treatment of infections caused by antimicrobial drug-resistant bacteria. The Innovative Medicines Initiative in Europe established the "New Drugs for Bad Bugs (ND4BB)" program and has strengthened efforts toward the resolution of scientific and regulatory problems or managerial issues that could be barriers to the development of new antimicrobial drugs in seven projects, including COMBACTE (Combatting Antibiotic Resistance in Europe) and ENABLE (European Gram Negative AntiBacterial Engine).

National measures now support efforts to avoid running out of countermeasures against antimicrobial drug-resistant bacteria, resulting in the significant understanding of this as a common problem to all humankind.

2. Issues and Measures

The major factors blocking in the way of the research and development of new antimicrobial drugs are the difficulty of searching for "seeds" of drug discovery, the difficulty in conducting clinical studies on drugs for the treatment of infections caused by antimicrobial drug-resistant bacteria, and the low profitability of antimicrobial drugs. Because the issues of clinical studies and profitability cannot be resolved through the efforts of pharmaceutical companies alone, governments must take measures to incentivize companies that develop drugs for the treatment of infections caused by antimicrobial drug-resistant bacteria. For example, the Generating Antibiotic Incentives Now Act of 2011 came into force in the United States with the aim of promoting drug discovery through incentives, including: [1] designation of innovative drugs for the treatment of infections, [2] priority review, [3] expedited approval and fast track system, and [4] extension of patent exclusivity period by 5 years. Furthermore, to effectively conduct clinical studies, discussion has been continued regarding convergence in clinical protocols and regulatory requirements under the cooperation between three regulatory authorities: the Pharmaceuticals and Medical Devices Agency, the European Medicines Agency, and the FDA.

Expected profits are necessary for pharmaceutical companies to energetically engage in research and development in the field of bacterial infections, and to achieve this, in addition to the above, the introduction of new incentive systems has been considered. This includes financial cooperation in the research and development step before approval, called push incentives; a system to ensure profitability for companies after approval, called pull incentives; and incentives that are a combination of those incentives. In particular, pull incentives are rather attractive for companies, and the following systems have been considered: payment of a reward based on developing or obtaining approval of new drugs for the treatment of infections caused by antimicrobial drug-resistant bacteria (market entry reward), extension of the exclusivity period for marketing in-house, non-antimicrobial products with the highest profitability (transferable exclusivity), and having public organizations store and purchase the new drugs for the treatment of infections caused by antimicrobial drug-resistant bacteria.

3. Sustainable Measures against AMR

A bacterium may accidentally own a gene that protects it from antimicrobial drugs and will vertically transmit this resistant gene to its descendant. Moreover, this gene can also be horizontally transmitted to nearby bacteria. The spread of the drug resistance in this way is an unavoidable natural phenomenon. Because the selective risk of antimicrobial drug

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resistance increases in association with the amount of antimicrobial drug use, such drugs should be properly used, considering the benefits such as curing an infection and the risks such as the selection of resistant bacteria. This differs from anticancer drugs that would be used for a long term or drugs for chronic diseases, including hypertension, hyperlipidemia, and diabetes mellitus. It is difficult for pharmaceutical companies to take on the responsibility of discovering new antimicrobial drugs that are important for global health by their own abilities under current rules in the circumstance that there is a risk for a shortened drug lifetime because of the emergence and spread of antimicrobial drug-resistant bacteria, the amount of use is small because of use restrictions to prevent the emergence of antimicrobial drug-resistant bacteria, and an ultra-high drug price would not be approved.

To take sustainable measures against antimicrobial drug-resistant bacteria from the point of view of the development of new antimicrobial drugs, an idea, called "de-linking from sales", which means de-linking the amount of use (sales amount) of antimicrobial drugs from the pharmaceutical company's profit due to the sales amount, is important. For example, the aviation industry, which was affected by the spread of infection due to a novel influenza virus in 2009, has recognized that countermeasures against infections are important. An idea utilizing new links between values has arisen; that is, using the international solidarity levy that would be imposed to international airline tickets as the resource for measures for infections. Furthermore, the realization of some measures that would change conventional concepts of pharmaceuticals are being considered: for example, changing the recognition of antimicrobial drugs from "a commodity to purchase" to "infrastructure shared by the people" and imposing a charge on prescriptions or a license fee on the use of antimicrobial drugs, just like computer software.

Project with the Kitasato Institute Utilizing the Collaboration of Industry, Academia, and Government

1. Cyclic Innovation for Clinical Empowerment

The AMED was established in April 2015 with the aim "to support research conducted by universities/colleges, research institutes, and other organizations, and address research and development and environmental improvement for them in order that basic-to-practical research and development in the field of medical care will be conducted continuously and their outcomes will be put to practical use smoothly". As one of the AMED's measures, a new project called CiCLE took off, using 55 billion yen from the supplementary budget, and invited applications for the first term in April 2017. CiCLE is a long-term, large-scale project at a cost of 0.1 to 10 billion yen for up to 10 years with the aim of sponsoring research and development for the practical application of pharmaceuticals, medical devices, regenerative medicine products, and medical technologies by various types of combinations between companies, universities/colleges, and other organizations, such as collaboration between industry and academia or between industries. CiCLE adopts a system of sharing risks between the AMED and companies, using the following scheme: milestones and goals of the project should be set together with the AMED, and the expenses for research and development commission should be returned if the goals have been achieved; otherwise, 10% of the expenses should be returned.

2. KS-Project

Based on the importance of the global problem of antimicrobial drug-resistant bacteria mentioned above, our company believed that the CiCLE project was a good opportunity for conducting discovery research on new drugs for the treatment of infections caused by antimicrobial drug-resistant bacteria. Thus, we applied for CiCLE with a research project entitled "Drug discovery research aiming at development of agents against infections with bacteria showing antimicrobial resistance (AMR)" jointly with Satoshi Omura, Distinguished Emeritus Professor, Kitasato Institute, who is one of the top researchers on infections in Japanese academia; and Hideaki Hanaki, Director of the Infection Control Research Center, and Toshiaki Sunazuka, Professor, Laboratory of Bioorganic Chemistry, both of whom were members of a drug discovery group led by Satoshi Omura. This survived the AMED's review admirably and was selected as one of the seven projects adopted from 48 application titles on July 2017. We named the joint research on the discovery of drugs for the treatment of infections caused by antimicrobial drug-resistant bacteria by Omura's drug discovery group and our company utilizing CiCLE, as the KS-Project (Kitasato-Sumitomo Dainippon Antimicrobial

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Resistance [AMR] Drug Discovery Project). We began a full-scale project in October 2017.

Satoshi Omura, Distinguished Emeritus Professor, was awarded the Nobel Prize in Physiology or Medicine in 2015, with Dr. William Campbell who was working at Merck, "for their discoveries concerning a novel therapy against infections caused by roundworm parasites". The outcome of the research, "ivermectin", a drug that treats a parasitic disease, has been used by 300 million people annually worldwide and is a specific medicine that relieves patients in Africa and Central and South America from fear of blindness. Omura's drug discovery group invented a new separation method for useful microorganisms and has discovered 42 new species, including 13 new genera. Furthermore, the group has established a new search system to identify bioactive organic compounds from isolated soil bacterium containing the microorganisms and has discovered over 470 new substances that interest us for both their structural and bioactive properties.[7] Among these substances, 26 natural substances or their derivatives have already been put to practical use as pharmaceuticals, veterinary drugs, agrochemicals, and reagents for studies.

We are expecting significant improvement in the probability of successful research and development of new drugs with high-level difficulty for the treatment of infections caused by antimicrobial drug-resistant bacteria by bringing together strengths from Omura's drug discovery group in the Kitasato Institute, which has the tradition and achievements to launch more than one drug for the treatment of infections, and our company, which has achievements in the research and development of antimicrobial drugs and the know-how of a pharmaceutical company. The details of the project are undisclosed; however, we are aiming to create drugs for the treatment of infections caused by antimicrobial drug-resistant bacteria that break conventional concepts and put them to practical use within 10 years. We are progressing to reach this goal from several different angles including the "effect on the mechanism of resistance", "inhibition of the mechanism of infection and pathogenic factors", "restoration of immune system of the host", and the "physical elimination of pathogenic bacteria". Satoshi Omura, Distinguished Emeritus Professor, is responsible for the overall supervision as the special coordinator of the project. Several researchers, including us (Hidaka and Takemoto), were dispatched from our company to the Kitasato Institute to organize a combined team with researchers from the Kitasato Institute, and the project is promoted under the overall research support of our company. Furthermore, the AMED instructs us through the CiCLE project; therefore, the project is a very open-innovation drug discovery research study operated by "all of Japan", including industry, academia, and the government.

Conclusion

Since the discovery of penicillin, there has been a spiral of development of new antimicrobial drugs and the emergence of antimicrobial drug-resistant bacteria. Unfortunately, the development of new antimicrobial drugs that are effective against antimicrobial drug-resistant bacteria has currently been a global exigency in which many pharmaceutical companies have withdrawn. We strongly believe that providing innovative drugs from this project is a responsibility of our company, which has achievements in the research and development of antimicrobial drugs; this will help achieve the "National Action Plan on Antimicrobial Resistance" in Japan, improve global health, and contribute to preventing economic loss.

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