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Message from the Chairperson

Keiji TANAKA

Tokyo is the political, economic and cultural center of Japan. Developing Tokyo into a more healthy welfare state will therefore go a long way toward building a prosperous future for Japan. The mission of the Tokyo Metropolitan Institute of Medical Science (TMIMS) is to promote research in the life and medical sciences to improve the lives and health of the citizens of Tokyo. It is well known that Japan has the most rapidly aging society in the world. Tokyo, which reflects Japan itself, is undergoing a steady increase in cancers and infectious diseases, lifestyle-related illnesses, neural and mental disorders, and various other health problems. Naturally, curing all of these diseases is a common goal for all humankind, and considerable efforts have been made at the national level. However, it is also essential for the Tokyo Metropolitan Government to take the initiative in this endeavor. Tokyo has numerous problems unique to megacities. For instance, many people suffer from rare and intractable diseases that researchers often overlook. TMIMS has been actively working on these important problems, promptly and practically addressing health-related issues with the aim of protecting the health of all Tokyo citizens.

In 2020, the highly contagious COVID-19 disease spread throughout the world causing unprecedented damage at all levels of society. Combatting this disease is a top priority. At TMIMS, we swiftly set up a "Coronavirus Countermeasures Special Team" last year and in cooperation with the Tokyo Metropolitan Government, we have been making every effort to develop effective strategies to eliminate this disease. However, unfortunately, the pandemic is still ongoing and TMIMS will need to continue fundamental research in order to develop effective countermeasures to combat the disease in 2021. Throughout history there has always been an ongoing struggle between humans and infectious diseases. In the 21st century, globalization and international human interactions have greatly accelerated academic development and the elucidation and dissemination of new knowledge. However, globalization has allowed the spread of infections at unprecedented speeds. Thus, it is critically important for people in the modern world to have effective strategies for preventing infectious diseases, minimizing their spread, and developing effective cures without curtailing international interactions. This has generated a strong social demand for medical advances and solutions. With this goal in mind, scientists at TMIMS will continue to dedicate themselves to advancing basic and clinical research.

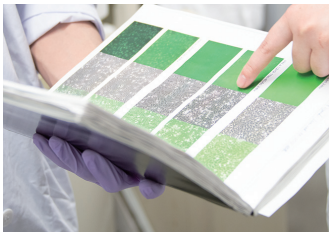
I am of the opinion that scientific research is a symbol of culture. A society cannot be considered cultured if it has no interest and knowledge of science and research. Accordingly, TMIMS aims to be acclaimed both academically and culturally for the knowledge and wisdom of its excellent researchers. Our goal is to become a symbol of the culture of Tokyo, the foremost megalopolis in the world. Academic research is often roughly divided into top-down, exit-oriented, applied research (of immediate use), and bottom-up, future-oriented fundamental research (seemingly not of immediate use). Balancing these two research strategies, TMIMS endeavors to operate in a flexible manner in order to achieve additive and synergistic effects. Top-down and bottom-up research strategies are not incompatible, but can work in a cooperative and harmonious manner. Throughout the history of science, we can find numerous examples of seemingly useless research suddenly becoming useful, resulting in great service to society.

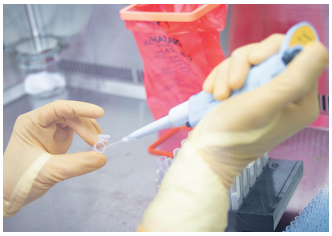
Our medical researchers are energetically pursuing their research to develop preventive medicine and new therapeutic methods to protect citizens' health. During this process, TMIMS also takes on a role in educating young researchers who will continue to develop human knowledge and contribute to social prosperity. All staff members of TMIMS are working on research in the life sciences, ranging from fundamental to practical, using cutting-edge technologies to achieve their goals.

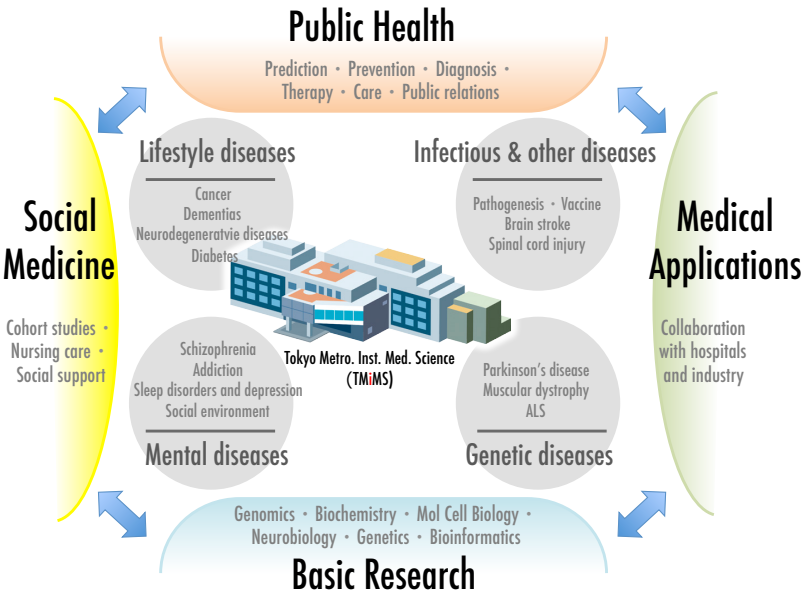
We are working to make TMIMS the world's premiere research institute, and advancing and enriching its research power will create an institute capable of providing wide-ranging services to society. To this end, the entire staff of TMIMS strives to help pursue incomparable fundamental research, and pass the benefits of this research on to society. At the same time, we are continuing to recruit and educate talented people to increase our momentum. Thank you for your support, which is indispensable for the further development of TMIMS.

Our Mission

The mission of TMIMS is to pursue research that will provide solutions for health-related problems commonly observed in large urban areas and developed countries. We pursue basic research to understand molecular and cellular mechanisms of biological pathways and disease pathology, and collaborate with municipal hospitals and clinics to translate basic research findings into technologies that can be used to predict, prevent, and treat health problems. Toward this goal, we try to identify causes of unsolved diseases in order to develop novel drugs and therapies. We study mental diseases to find effective treatment, and investigate social factors that affect mental health of people in urban area. We also contribute to improved care for those suffering from incurable diseases such as ALS to better patients' quality of life.







Message from the Director: TMIMS 2020

Hisao MASAI

2020 marks the 9th anniversary of the founding of the Tokyo Metropolitan Institute of Medical Science (TMIMS) from the merger of three medical institutes that had been operated independently by the Tokyo Metropolitan Government for more than 35 years. This year would have been more celebratory for us, but for the unprecedented and devastating pandemic which has affected all people on earth. 2020 started peacefully with much anticipation in Tokyo for the upcoming Olympics, but ended in a struggle to overcome the pandemic which is still ongoing.

The outbreak of COVID-19 will likely irreversibly change our way of life. We will have to learn to live with this virus and others from now on. What is different now compared to 100 years ago when the Spanish flu infected 600 million and killed 20-40 million people is that we now have better scientific tools with which we can scrutinize viruses, prevent infections, treat infected patients, analyze infection patterns, and predict the future spread.

What can we do to combat COVID-19?

As scientists working in the field of medical science, it is our responsibility to join worldwide efforts to understand the pathological mechanisms of viral spread, elucidate the causes of severe cases, develop drugs to counterattack viral proliferation and treat infection-associated symptoms, and develop effective vaccines. Indeed, we have organized a special project team in our institute to combat COVID-19. This team is composed of three research/ development groups; vaccine development, antibody screening, and interdisciplinary research.

1 Vaccine development: We are developing SARS-CoV-2 vaccines based on vaccinia virus vectors which will induce immunological responses that are longer lasting and more versatile in dealing with ever changing viruses. We are now at the stage of non-clinical testing and will start clinical testing in 2021.

2 Antibody screening: In collaboration with 14 hospitals in the Tokyo Metropolitan district, we have been monitoring SARS-CoV-2 antibodies in the general populace to track and monitor infections. We initiated this project in June and have accumulated data for more than 20,000 people in the Tokyo Metropolitan area. Data are reported to the Tokyo Metropolitan Government in order to design and develop effective policies for preventing the spread of infections.

3 Interdisciplinary research: Interdisciplinary research includes analyses of interactions between cellular glycolipids and the viral Spike protein, development of novel anti-virus drugs targeting the RNA genome, searches for genetic factors that contribute to serious cases, development of vaccine adjuvants that boost vaccine efficacy, and proteomic analyses of host responses to virus infection.

The team also includes various support groups as well as a

public relations group which reports important up-to-date scientific news regarding COVID-19 on our homepage to enlighten the general public.

In addition to these efforts, we are helping the newly established Tokyo iCDC (Centers for Disease Control and Prevention) by providing board members with expertise in viral infections, vaccine development, and statistical analyses of infectious spread.

Despite several hundred papers published every day, SARS-CoV-2 is still far from being completely understood. Why does SARS-CoV-2 cause only mild effects in children? Why are elderly people more prone to serious cases? Are antibodies against SARS-CoV-2 short-lived? Why can some people be reinfected by the virus? What are the host factors that contribute to severe infections? How do viral mutations affect transmissibility? We are currently examining these questions in order to help combat this disease and bring back the life we enjoyed pre-COVID-19.

The start of a new project term

Research at TMIMS is organized into projects with 5-year goals. The 3rd project term ended in March 2020 and the 4th term started this year. We currently have 21 projects and 6 laboratories organized in four departments: Basic Medical Sciences, Brain & Neurosciences, Psychiatry & Behavioral Sciences, and Diseases & Infections. We also established the Research Center for Genome & Medical Sciences in 2020. This center will focus on informatics analyses of genomes for both basic research and for collaborative research with hospitals aimed at developing novel diagnostic and therapeutic tools. The Research Center for Social Science & Medicine was also launched in 2020 to improve our research in social medicine using long-term cohort studies. The establishment of these centers will enable us to conduct projects that require support for longer terms and allow us to deal with problems in a more flexible manner.

Our recent findings

During the 3rd project term, Chiaki Maruyama discovered a novel role of subplate neurons in development of the six-layered structure of the cerebral cortex. She discovered that these neurons form temporary synaptic connections with recently born neurons to control their migration. This work was published in Science. Yukio Nishimura and colleagues discovered that the primary somatosensory cortex receives information about motor output even before the arrival or sensory feedback signals, suggesting that this cortex receives anticipatory information with which it can process somatosensory signals. Keisuke Kamimura found that Glypican, a heparin sulfate peptide glycan, is required for experience-dependent synaptic and behavioral plasticity. This work demonstrates the importance of extracellular matrix proteins in behaviors. Tomoyuki Miyashita and Minoru Saitoe identified cellular mechanisms by which repeated trainings establish long-term memory engram cells, an important breakthrough in understanding how memories are formed and stored in the brain. Hikaru Tsuchiya analyzed different types of ubiquitin linkages and found that the Cdc48-Rad23/Dsk2 axis is responsible for directing certain types of ubiquitin-linked substrates to proteasome-dependent protein degradation. Yukiko Yoshida uncovered a novel mechanism by which damaged lysosomes are recycled in cells. These damaged lysosomes release glycosylated polypeptides which are then ubiquitinated and target lysosomes for autophagic degradation. Yutaka Kanoh analyzed G-quadruplex structures on genomes and discovered that they are important elements for generating higher-order nuclear architecture and for regulating DNA replication timing by binding to the Rif1 DNA binding protein.

Achievements in 2020

In the 4th research term we have continued making important findings. Yasushi Saeki and colleagues continued their work on protein ubiquitination and proteasome-dependent protein degradation and found that under stressful conditions, where cells have to increase protein degradation, proteasomes and ubiquitinated substrates form liquid droplets where protein degradation occurs. This concentration of protein degradation to specific nuclei likely enhances efficiency of degradation (featured in "Meet our scientists!"). Masato Hasegawa, in collaboration with the MRC Laboratory of Molecular Biology in Cambridge, UK, reported the structures of α-synuclein filaments from different human neurodegenerative diseases. This work shows how non-genetic changes in one protein can cause distinct diseases with different symptoms. The results from the Saeki and Hasegawa projects were both published in Nature. Akihiro Yamano discovered that the optineurin-ATG9 axis is important in degradation of damaged mitochondria, shedding new light on cellular pathways by which old or non-functional organelles are recycled in cells (featured in "Meet our scientists!"). Syudo Yamazaki and Atsushi Nishida in collaboration with a group from London University, UK, analyzed the results of a 60 year cohort study and found that adolescents who actively pursued their aspirations, curiosity and interests expressed greater life satisfaction at early old ages. Akiyo Natsubori and Makoto Honda discovered that intracellular ATP levels oscillate during sleep-wake states in mouse cortical excitatory neurons. They found that ATP levels significantly decrease during REM sleep cycle, suggesting that energy consumption increases during this period of sleep.

Despite the COVID-19 pandemic, we have also continued our outreach activities, conducting five public lectures and three science café educational programs online. With the uncertain outlook for the coming year, we will continue to expand and improve our online lectures to educate the public on the importance and excitement of science and research.

Outlook for 2021

Cutting-edge basic medical research will continue to be the key to the understanding various diseases, developing preventive and therapeutic measures, and improving physical and mental health. The strength of our institute is the presence of experts in wide areas of life sciences and medical sciences who enjoy research and work together to discover previously unknown biological phenomena for the benefit of all people. In 2021, we will continue to strive for new discovery that will contribute to the health and welfare of the public.

Team Director, Special Team for COVID-19 Countermeasures

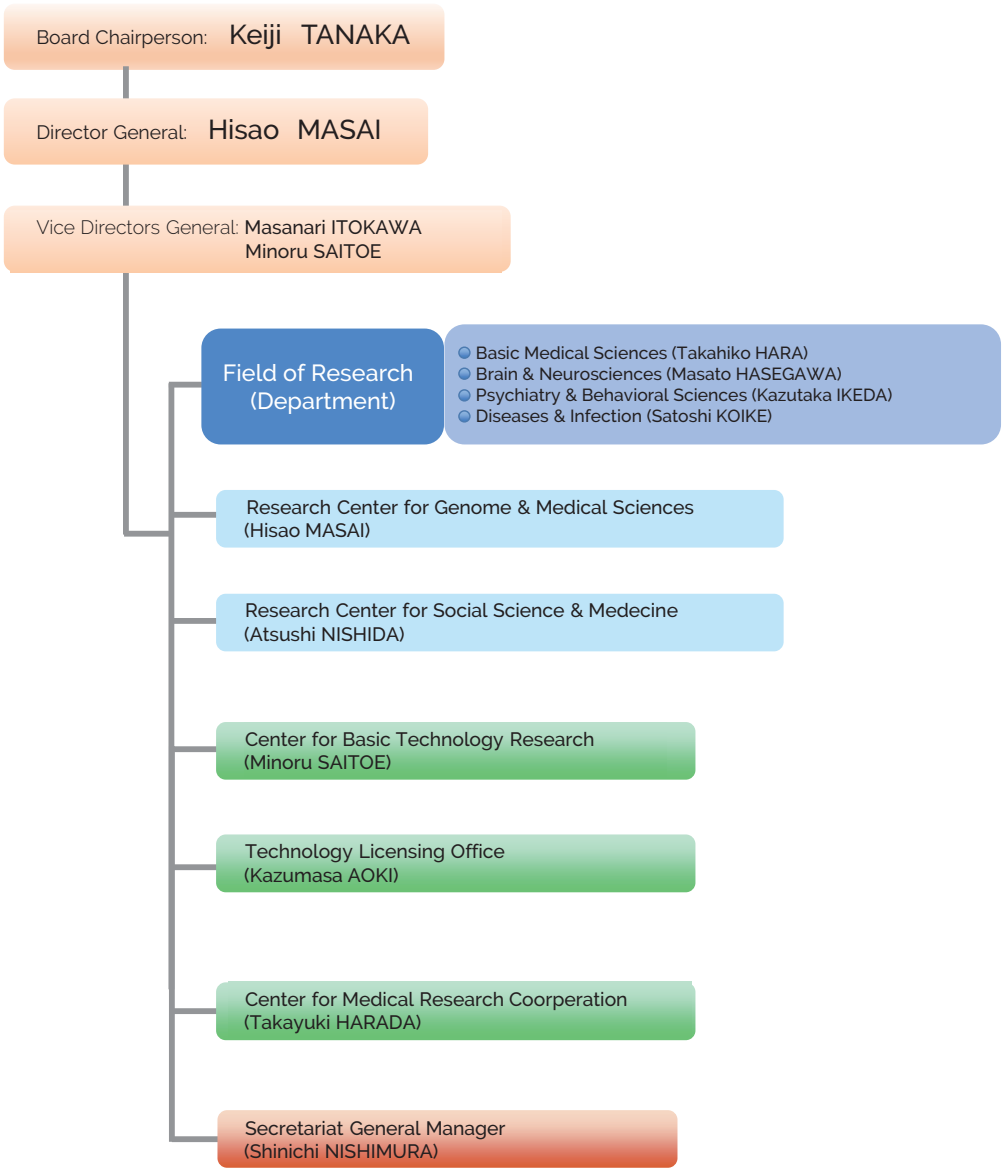
Vice Director General
Masanari ITOKAWA

The recent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused a worldwide public health emergency. However, SARS-CoV-2 is just the latest of various epidemics and pandemics that have plagued us throughout history. In his "Vitae Parallelae," Plutarch describes the three Cs of, closed spaces, crowded places and close-contact settings that influence contagions, demonstrating humankind's long and ongoing efforts to combat disease transmission. In addition, many types of folklore and traditional tales have been handed down describing the correct behaviors for preventing the spread of disease. The differences between our responses to recent infections compared to those of the past is that since the beginning of bacteriology in the 19th century, we can utilize our knowledge that infectious phenomena are caused by small invisible organisms such as bacteria and viruses.

TMIMS is an organization consisting of over 100 scientists. We are working to address the SARS-CoV-2 pandemic by vastly increasing the collaborative efforts of our medical research teams and increasing the support from our administrative offices and support divisions. As a Tokyo Metropolitan Institute, we are coordinating the largest hospital cooperative effort in Tokyo to date encompassing 7,000 beds in 14 metropolitan and public hospitals in order to protect the citizens of Tokyo from this pandemic.

Joint Meeting of the Task Forces for Antibody Testing and Research Support

Organizational Chart



Our People at a Glance

Position	Number
Researchers	163
Postdoctoral Fellows	51
Students	152
Visiting Scientists	144
Guest Scientists	145
Administrative Staffs	27
Total	682

January 1, 2021