Introduction To

TMiMS

Tokyo Metropolitan Institute of Medical Science
Mechanisms of Stable Maintenance and Inheritance of Genome

Identification of Pathogenic Mechanisms Underlying Mammalian Genetic Diseases

The Tokyo Metropolitan Institute of Medical Science (TMIMS) was established in April 2011 from the merging of three institutes; the Tokyo Metropolitan Institute for Neuroscience, the Tokyo Metropolitan Institute of Psychiatry, and the Tokyo Metropolitan Institute of Medical Science. These three institutes had all been founded in the early to mid-1970s with the support of the Tokyo Metropolitan Government, but had been separate entities located in different areas of Tokyo. With the merger, scientists from three different disciplines came together in a new spacious research facility in a quiet residential area in Kamikitazawa in Setagaya-ku, about 15 minutes by train from Shinjuku. The institute is under continuous support from the Tokyo Metropolitan Government, and we are striving to advance medical research and improve the health and welfare of people living in metropolises through collaborative research in basic life sciences, medical sciences, social medicine, and nursing. This booklet introduces the research being pursued in our 27 research projects and 3 laboratories with support from other divisions that provide services including research facilities/technical assistance, technology transfer licenses, and collaboration with hospitals.

Many common diseases, such as age-related hearing loss, atopic dermatitis and cataract, are caused by a combination of genetic and environmental factors. Environmental effects cannot be completely excluded in genetic analyses of these diseases in humans. We are trying to identify genes associated with diseases such as age-related hearing loss, atopic dermatitis, and cataracts using both forward and reverse genetic approaches in mice.

Approaches for identification of pathogenic mutations

Forward genetics
- Linkage & QTL mapping, GWAS, expression QTL
- Phenotypes
- Genes

Reverse genetics
- Genome editing, transgenesis

Message from Our Director

"We are trying to decipher 'unexplored messages' of the genome that are crucial for shaping chromosomes, and copying and reading genetic information. Defects in these messages cause various diseases."

Hisao Masai
Yoshiaki Kikkawa
We have shown that antigen-specific Tregs stimulate Th17-mediated inflammation in a CTLA4-dependent manner. This finding calls into question the efficacy of Treg/CTLA4-based immunological treatments for inflammatory diseases.

"We are developing new diagnostic methods and treatments for allergies"

1. Investigation of molecular mechanisms of sublingual immunotherapy (SLIT) and development of therapeutic biomarkers for allergic diseases.

2. Antigen-specific iTreg cells stimulate Th17-mediated colon inflammation

Development of suitable animal models for incurable viral diseases

Development of a suitable animal model for Enterovirus 71 infection

Fusing cancer cells to MSCs increases metastasis

Diagnostics for cancers and infectious diseases
Dementia Research Project
Molecular Mechanisms of Progressive Neurodegenerative Dementia

Our goal is to develop novel neuro-rehabilitation methods to restore functions lost after damage to the central nervous system.

Learning and Memory Project
Mechanisms of Learning and Memory in Drosophila

We visualize neuronal activity in the mushroom bodies under a microscope while flies are learning (left). We also study learning-associated neuronal plasticity in isolated brains (right).

Neural Prosthesis Project
Restoring Lost Function After Neural Damage

Evolvability hypothesis
Physiological (Reproduction)

Pathological (Action)
Adiponectin suppresses neurodegeneration
Drosophila molecular genetics
**Developmental Neuroimmunology Project**

*Homeostasis in Brain Development*

“Towards a better understanding of neuro-immune interactions in the developing brain.”

“Towards a better understanding of neuro-immune interactions in the developing brain.”

“Towards a better understanding of neuro-immune interactions in the developing brain.”

**Synaptic Plasticity Project**

*Abnormal Synaptic Plasticity and Brain Diseases*

“Normal vs Neuro-developmental disorders”

“Model Mice Behaviors”

“Memory Engram Dynamics”

“Synaptic Morphology”

“Compound Screening”

“Preclinical & Clinical Trials”

“Mechanistic Studies on Synaptic Proteins”

**Neural Development Project**

*Molecular and Cellular Mechanisms of Neural Development*

“RP58 is a transcriptional repressor required for development of the cerebral cortex. RP58-deficient mice are defective for cell-cycle exit of progenitor cells, neuronal radial migration, and maturation of cortical neurons.”

**Neural Network Project**

*Mechanisms of Neural Network Formation and Dysfunctions in Neurodevelopmental Disorders*

“Neural Network Formation in Drosophila”

“Neuronal Migration in the Mammalian Neocortex”

Our major projects include:

1) Understanding the role of RP58 in brain development and maintenance

2) Identification of nutritional factors that alter brain development and function

3) Understanding the roles of environmental factors in development and aging of brain functions
**Mental Health Promotion Project**
Prevention, Treatment, and Rehabilitation for Promoting Mental Health

**Schizophrenia Research Project**
Characterization of the Etiology of Schizophrenia and Development of Treatments and Preventive Measures

- Pathophysiological and clinical association of Schizophrenia with carbonyl stress
- Development and analysis of mouse models based on Schizophrenia pathophysiology
- Clinical investigation of the effects of a vitamin B6 derivative in patients with carbonyl stress-related Schizophrenia
- Schizophrenia cell models and genetic counseling

**Affective Disorders Project**
Identification of the Etiologies of Affective Disorders and Development of Novel Treatments

**Sleep Disorders Project**
Narcolepsy and Hypersomnia: Find the causes to develop better treatments
Addictive Substance Project

Identification of Mechanisms Underlying Addiction and Development of Novel Treatments

Kazutaka Ikeda

Addictive drugs are invaluable for the treatment of pain and various developmental disorders/psychiatric diseases. However, addiction is a harmful and tragic side effect. We are studying the relationship between pain, addiction and developmental disorders in order to prevent/improve treatments for addiction.

Calpain Project

Exploring Calpain-mediated Biological Modulation in Health and Disease

Yasuko Ono

Calpain (CAPN) modulates the functions of various proteins by precise proteolytic processing. We study how defects in CAPNs cause various diseases, and aim to translate our findings into improvements in human health.

Ubiquitin Project

Ubiquitin Signaling and Ubiquitin-related Disorders Project

Noriyuki Matsuda

PINK1 and Parkin are proteins associated with Parkinson’s disease. When mitochondria are damaged (1), PINK1 and Parkin ubiquitylate these damaged mitochondria (2). Consequently mitochondria are engulfed in autophagosomes (3), which then fuse with lysosomes (4). This causes selective degradation of damaged mitochondria by a type of autophagy known as mitophagy(5). We study the molecular mechanisms underlying this process.

Stem Cell Project

Stem Cell-based Blood Regeneration and Cancer Therapy

Takahiko Hara

Goal 1: To increase production of hematopoietic stem cells (HSCs) from human iPSCs for transplantation therapy.

We found that forced expression of a transcription factor Lhx2 leads to robust ex vivo production of HSC-like cells from mouse ESCs/iPSCs (Blood 117: 3748-58, 2011).

Goal 2: Development of a drug that strengthens anti-cancer immune functions in humans.

We found that a chemokine, CXCL14, carries CpG DNA into dendritic cells. This causes activation of the TLR9 signaling pathway, which is effective in immune-suppression of cancers (EBiomedicine 24: 247-256, 2017).

Kazutaka Ikeda

Noriyuki Matsuda

Takahiko Hara

Yasuko Ono
Regenerative Medicine Project
Development of Novel Therapies for Genetic Disorders by Genome Editing in iPS Cells

Stroke Renaissance Project
The Elucidation of Mechanisms Underlying Inflammation and Repair After Stroke

Laboratory of Protein Metabolism
Elucidation of Fundamental and Pathophysiologic Mechanisms of the Ubiquitin-Proteasome System

Laboratory of Biomembrane
Physiological Functions of Lipid Rafts / Glycosphingolipid Microdomains in Transmembrane Signalings

Yasushi Saeki
Yuichiro Miyaoka
Takashi Shichita
Kohji Kasahara

Elucidation of Fundamental and Pathophysiological Mechanisms of the Ubiquitin-Proteasome System

- Dynamics and pathophysiology of the proteasome
- Roles of specialized proteasomes in cell-mediated immunity
- Deciphering the ubiquitin code
- Developing innovative strategies for treatment of UPS-related diseases

Research Projects

- Development of novel therapies for genetic disorders by genome editing in iPS cells

- The Ubiquitin-Proteasome System (UPS)
  - Ubiquitin controls the fate of over 5,000 proteins
  - UPS dysfunction causes various diseases

- Sterile inflammation after ischemic stroke
  - What is the trigger of neural repair?

- Our mission is to develop therapeutics for stroke by integrating techniques from immunology, neuroscience, and molecular biology.
From neurons to motor control to brain disorders

We are trying to understand brain function. The brain first evolved to control movement and only later evolved to control higher brain functions.

Therefore, brain mechanisms for motor control must provide a basic framework for understanding higher brain functions.

The brain is an assembly of neural networks.

Optimization of Nursing Care and Community Based Management for Incurable Diseases

ALS Nursing Care Project

Diabetic Neuropathy Project

Therapeutic Approaches to Diabetic Neuropathy: Mechanistic Links between Metabolic Dysfunctions and Neurodegenerative Diseases

Neuroprotection

Neuroregeneration

Therapeutic strategies for retinal neurodegenerative diseases

New animal disease models

Drug repositioning


Hyperglycemia

Reduced Insulin Action

Atherosclerosis

Lipotoxicity

Polyol Pathway

Hexosamine Pathway

PKC Pathway

Glycation

Oxidative Stress

Nerve Ischemia

Peripheral Neuropathy

Protein Aggregation

(Brain)

Neurodegenerative Diseases

Matrix Metalloproteinase

In Vivo Models

DRG Neurons Immortalized Schwann Cells

Drosophila Models

In Vitro Models
Translating the Fruits of Basic Research into the Seeds of Clinical Treatments

The Basic Technology Research Center (BTRC) provides multiple resources and services required for research activities.

Technology Licensing Office (TLO)

The Technology Licensing Office (TLO) facilitates the conversion of scientific discoveries into innovative technologies with the ultimate goal of improving public health and welfare.

Slide Library and Digital Archive of Neuropathologies

The laboratory of neuropathology has more than 5000 sets of slides generated from the autopsied brains of people with various neurological diseases. We have been scanning these slides using virtual slide instruments to generate composite digital slides of various neuropathologies.

Making the dream of scientists a reality – from bench to bed and back again –

We provide advice on statistical analyses and pharmaceutical studies. We also provide ethical advice for studies involving human patients and human specimens. We connect scientists with medical doctors to facilitate clinical collaborations.

Many discoveries in science are made fortuitously, and it requires an open mind, free from bureaucratic obligations to see the importance and potential of these discoveries. We provide tools to determine whether findings from the bench can be developed into useful medical technology. Our work is akin to polishing a mined ore into a sparkling gem.
Tokyo Metropolitan Institute of Medical Science

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AIRPORT to INSTITUTE

- From Narita Airport to Kamikitazawa Station / Hachimanyama Station
  - Narita Airport - Shinjuku Station: JR Narita Express
  - Shinjuku Stellon - Kamikitazawa Station / Hachimanyama Station: Keio Line

- From Haneda Airport to Kamikitazawa Station / Hachimanyama Station
  - Haneda Airport - Shinagawa Station: Keikyū Line
  - Shinagawa Station - Shinjuku Station: JR Yamanote Line
  - Shinjuku Stellon - Kamikitazawa Station / Hachimanyama Station: Keio Line

From Kamikitazawa Station to the Institute
Walk (approx. 10 min from the South entrance of the station).

From Hachimanyama Station to the Institute

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<th>Kamikitazawa 2-chôme - Institute</th>
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