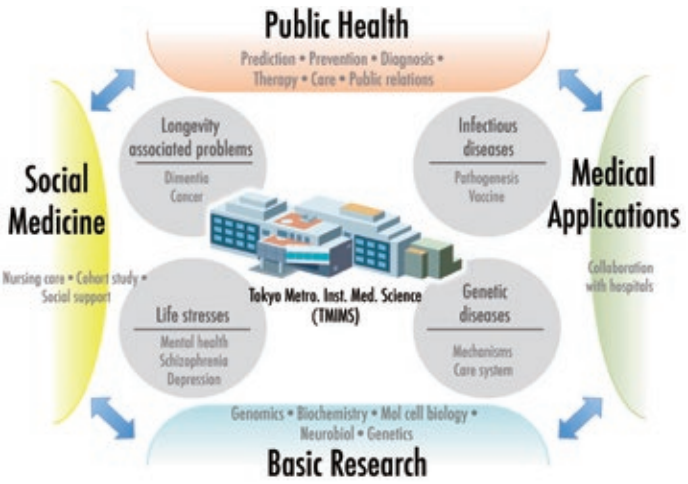
Introduction To

TMiMS

Tokyo Metropolitan Institute of Medical Science

Message from Our Director



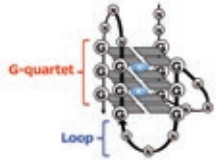
The Tokyo Metropolitan Institute of Medical Science (TMIMS) was established in April 2011 from the merging of three institutes; the Tokyo Metropolitan Institute for Neuroscience, the Tokyo Metropolitan Institute of Psychiatry, and the Tokyo Metropolitan Institute of Medical Science. These three institutes 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.

Genome Dynamics Project

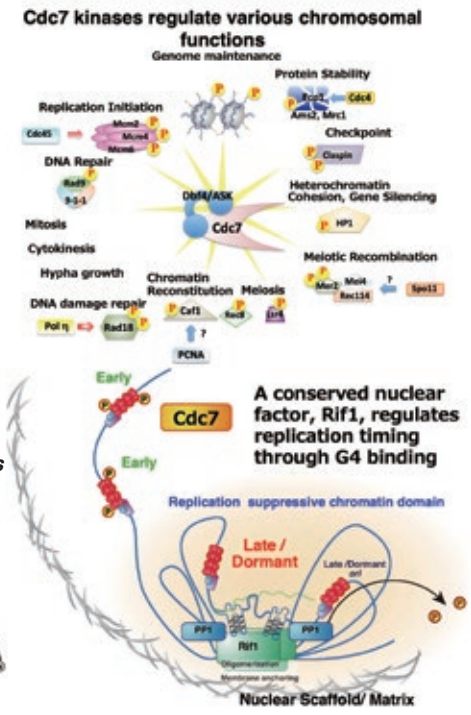
Mechanisms of Stable Maintenance and Inheritance of Genome

Hisao Masai

"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."



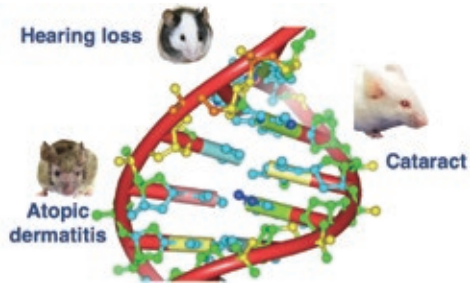
G-quadruplex (G4)



Mammalian Genetics Project

Identification of Pathogenic Mechanisms Underlying Mammalian Genetic Diseases

Yoshiaki Kikkawa



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**

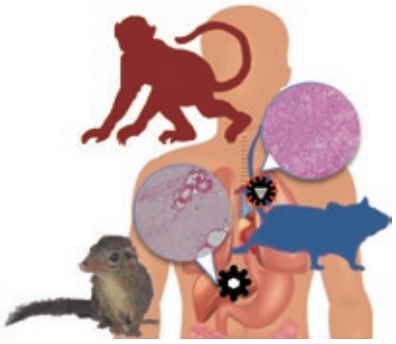
Reverse genetics
Genome editing, transgenesis

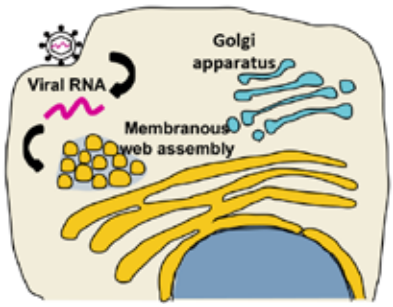
Viral Infectious Diseases Project

Prevention and Treatment of Infectious Viral Diseases

Fumihiko Yasui

Development of suitable animal models for incurable viral diseases





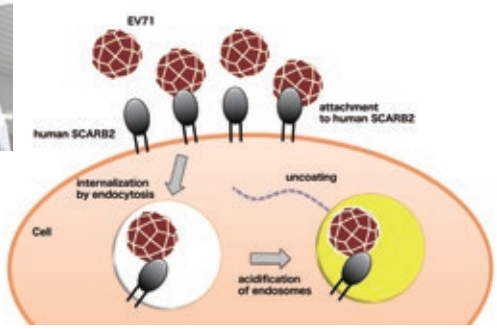
Focus on host antiviral responses vs. viral replication

Neurovirology Project

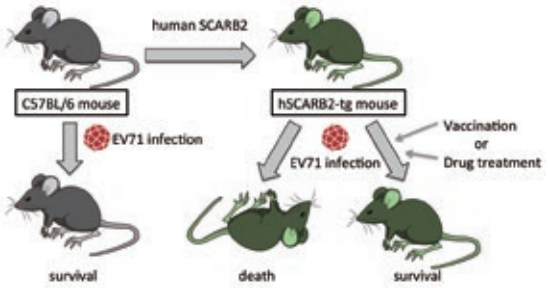
Development of Novel Therapeutics that Block Viral Infectivity

Satoshi Koike

Mechanism of Enterovirus 71 infection



Development of an animal model for Enterovirus 71 infection



Allergy and Immunology Project

Development of Mucosal Immunotherapies for Allergic Diseases

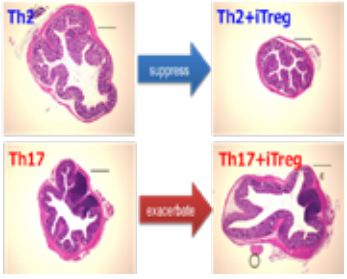
Takachika Hiroi

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

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

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

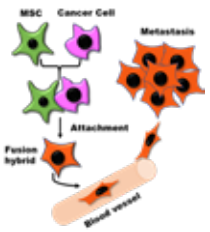
We have shown that antigen-specific Tregs stimulate Th17-mediated inflammation in a CTLA4-dependent manner. This finding calls into question the efficacy of Treg/CTLA4-based immunological treatments for inflammatory diseases.



Molecular Medical Research Project

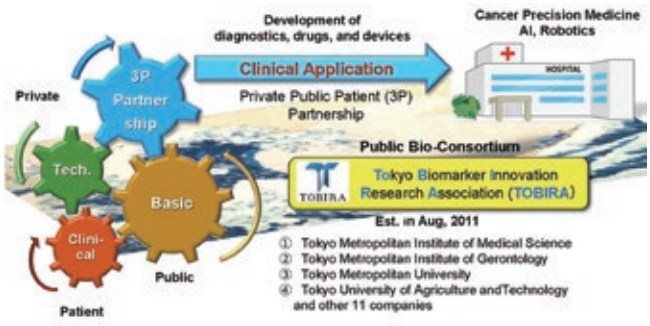
Identification of Molecular Targets of Cancers and Infectious Diseases – Medical Applications

Futoshi Shibasaki



Fusing cancer cells to MSCs increases metastasis

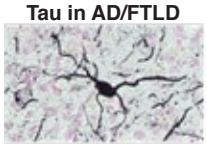
Diagnostics for cancers and infectious diseases

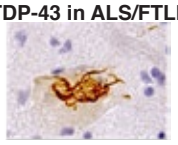


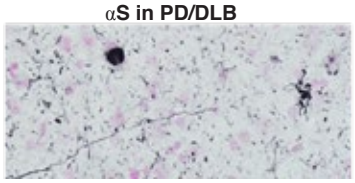
Dementia Research Project

Molecular Mechanisms of Progressive Neurodegenerative Dementia

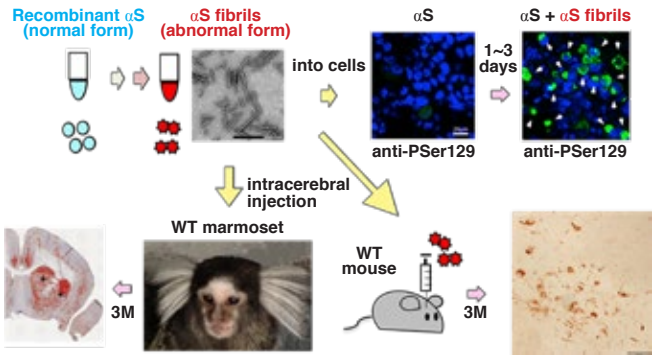
Masato Hasegawa







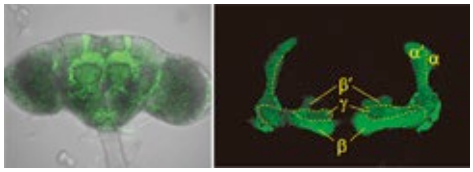
Cellular and animal models



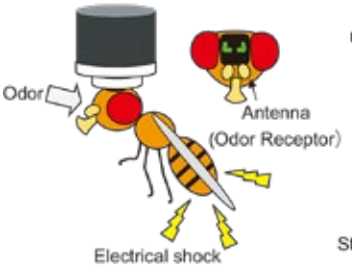
Learning and Memory Project

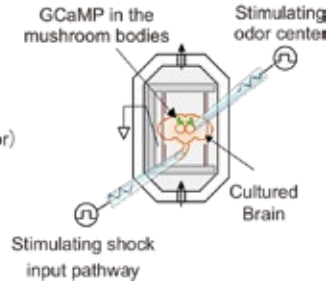
Mechanisms of Learning and Memory in *Drosophila*

Minoru Saitoe



The fly brain and the mushroom bodies where associative memories are formed and stored





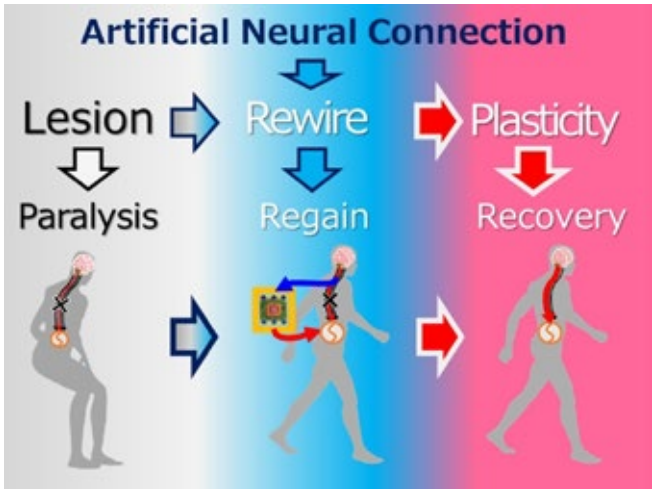
We visualize neuronal activity in the mushroom bodies under a microscope while flies are learning (left). We also study learning-associated neuronal plasticity in isolated brains (right).

Neural Prosthesis Project

Restoring Lost Function After Neural Damage

Yukio Nishimura

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

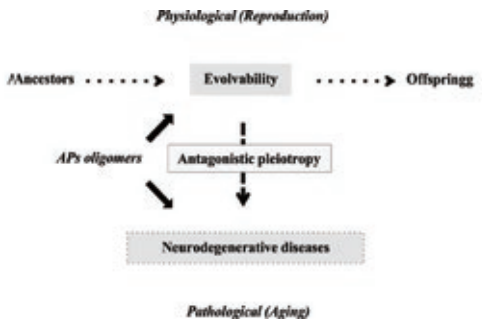


Laboratory of Parkinson's Disease

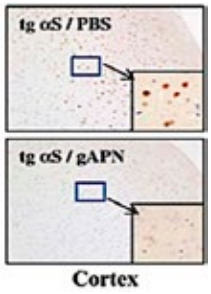
Development of Treatments for Neurodegenerative Diseases

Makoto Hashimoto

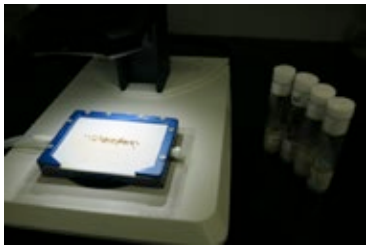
Evolvability hypothesis



Adiponectin suppresses neurodegeneration



***Drosophila* molecular genetics**

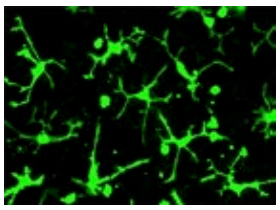


Developmental Neuroimmunology Project

Homeostasis in Brain Development

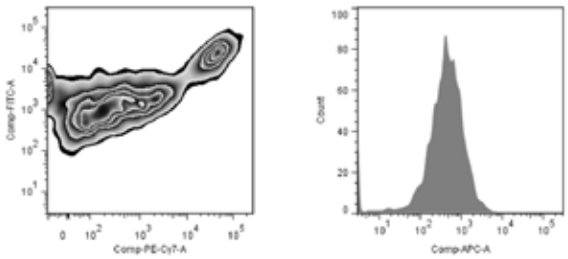
Hiroshi Sakuma

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



Microglia from CX3CR1-EGFP mice

"We are investigating the mechanisms by which microglia maintain homeostasis in the developing brain."

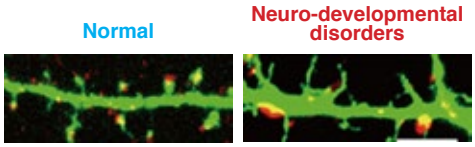


Flow cytometric analysis of microglia

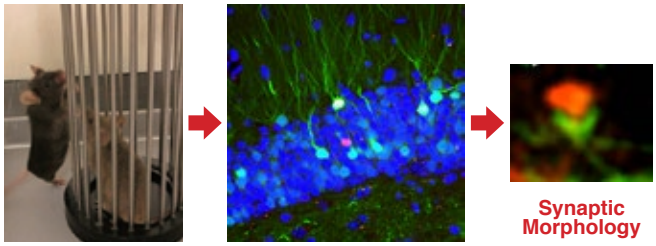
Synaptic Plasticity Project

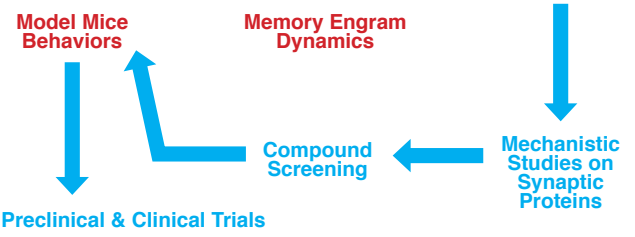
Abnormal Synaptic Plasticity and Brain Diseases

Kanato Yamagata



Synapse are not properly formed in neurodevelopmental disorders.

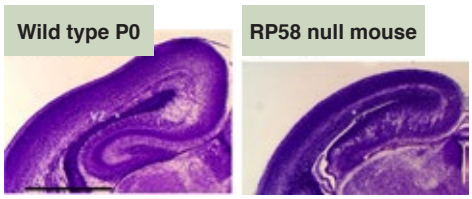




Neural Development Project

Molecular and Cellular Mechanisms of Neural Development

Haruo Okado



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.

"We are trying to understand how genetic and environmental conditions affect the molecular mechanisms of brain development and maintenance. This will help develop new treatments for neural and mental diseases."

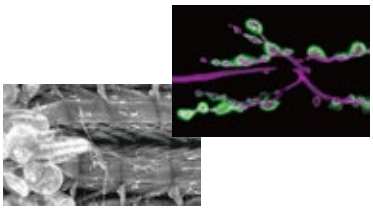
Our major projects include

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**

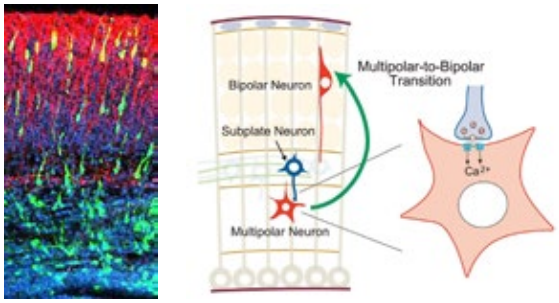
Neural Network Project

Mechanisms of Neural Network Formation and Dysfunctions in Neurodevelopmental Disorders

Chiaki Maruyama



Neural Network Formation in *Drosophila*



Neuronal Migration in the Mammalian Neocortex

Mental Health Promotion Project

Prevention, Treatment, and Rehabilitation for Promoting Mental Health

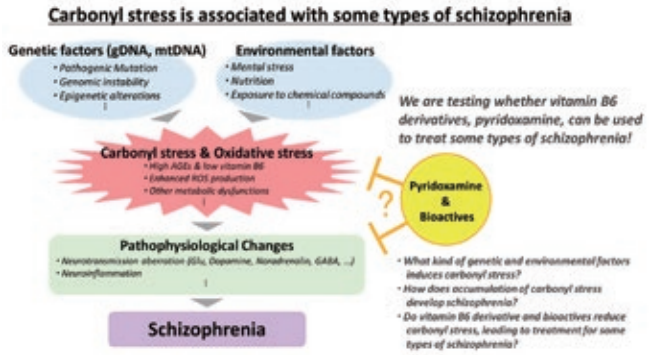
Atsushi Nishida

Schizophrenia Research Project

Characterization of the Etiology of Schizophrenia and Development of Treatments and Preventive Measures

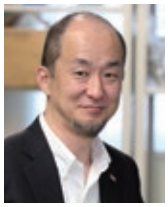
Makoto Arai

- 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

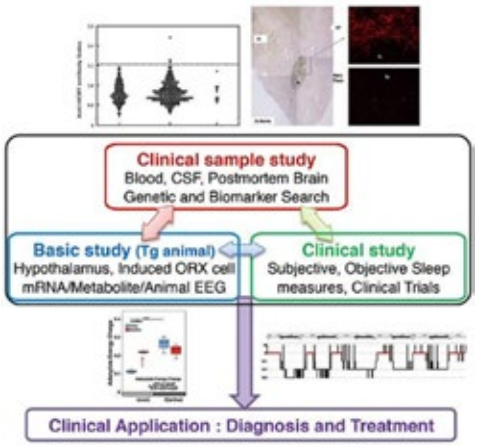


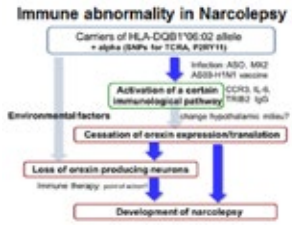
Yoshitaka Tatebayashi

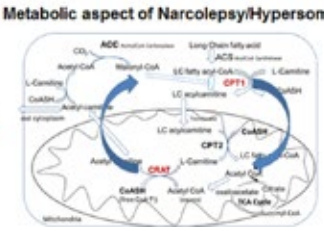
Sleep Disorders Project

Narcolepsy and Hypersomnia : Find the causes to develop better treatments

Makoto Honda







Addictive Substance Project

Identification of Mechanisms Underlying Addiction and Development of Novel Treatments

Kazutaka Ikeda

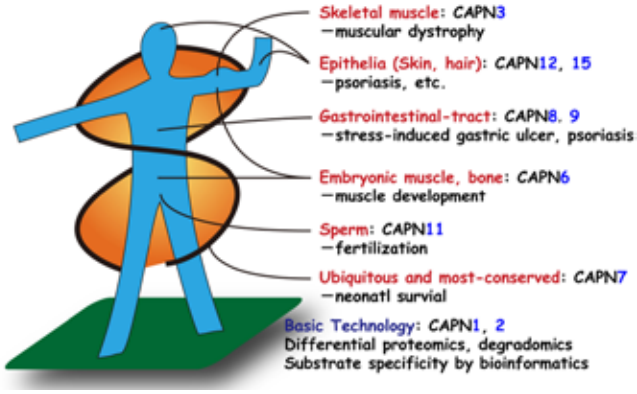
Addictive drugs are invaluable for the treatment of pain and various developmental disorders/ psychiatric diseases. However, addiction is a harmful and tragic side effect. We are studying the relationship between pain, addiction and developmental disorders in order to prevent/improve treatments for addiction.

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.

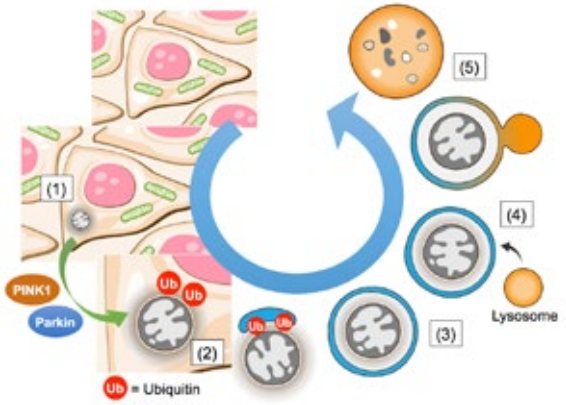


Ubiquitin Project

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.



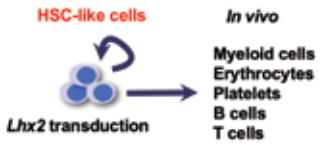
Stem Cell Project

Stem Cell-based Blood Regeneration and Cancer Therapy

Takahiko Hara

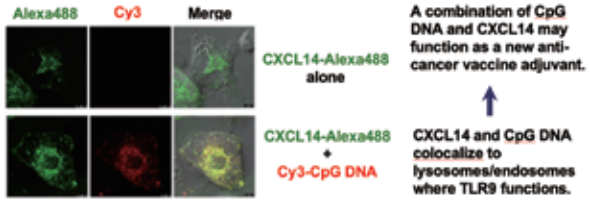
Goal 1: To increase production of hematopoietic stem cells (HSCs) from human iPSCs for transplantation therapy.

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.

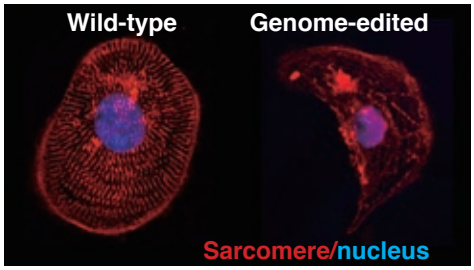
We found that a chemokine, CXCL14, carries CpG DNA into dendritic cells. This causes activation of the TLR9 signaling pathway, which is effective in immune-suppression of cancers (EBiomedicine 24: 247-256, 2017).



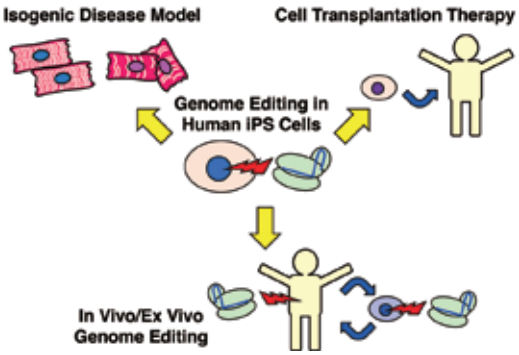
Regenerative Medicine Project

Development of Novel Therapies for Genetic Disorders by Genome Editing in iPS Cells

Yuichiro Miyaoka



Cardiomyopathy model in iPS cell-derived cardiomyocytes

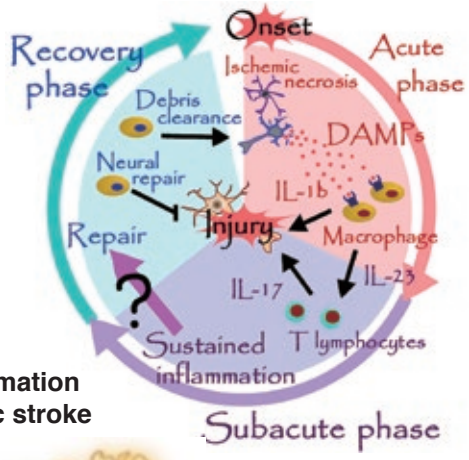


Genome editing in iPS cells to study and cure disease

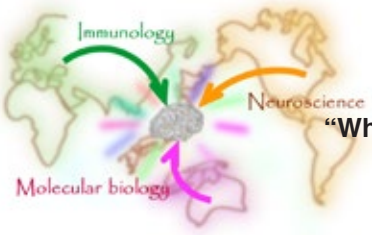
Stroke Renaissance Project

The Elucidation of Mechanisms Underlying Inflammation and Repair After Stroke

Takashi Shichita



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.

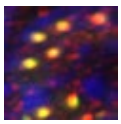
Laboratory of Protein Metabolism

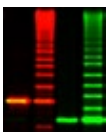
Elucidation of Fundamental and Pathophysiological Mechanisms of the Ubiquitin-Proteasome System

Yasushi Saeki

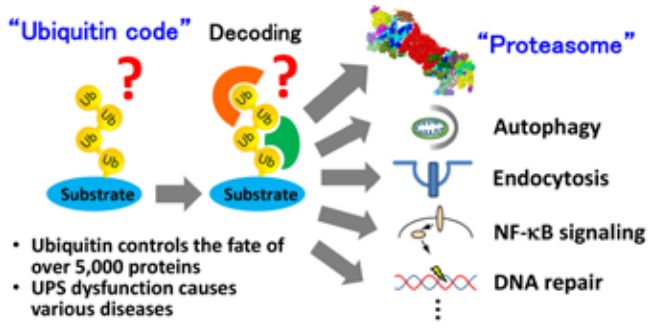
Research Projects

- 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





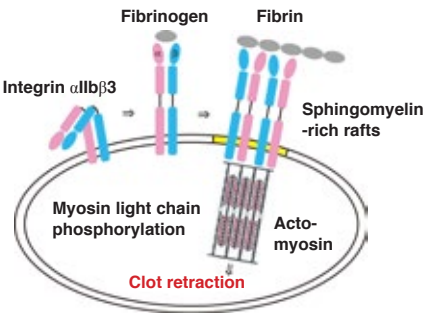
The Ubiquitin-Proteasome System (UPS)



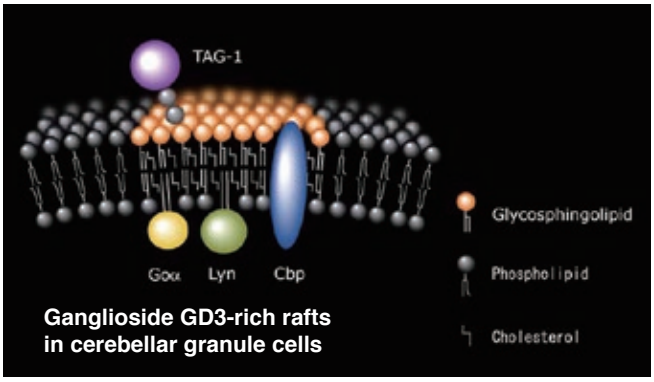
Laboratory of Biomembrane

Physiological Functions of Lipid Rafts / Glycosphingolipid Microdomains in Transmembrane Signaling

Kohji Kasahara



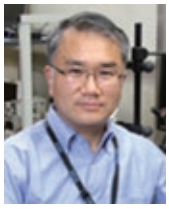
Sphingomyelin-rich rafts in platelets



Ganglioside GD3-rich rafts in cerebellar granule cells

Motor Disorders Project

Development of Higher Precision Tools for Evaluation of Neurological Disorders

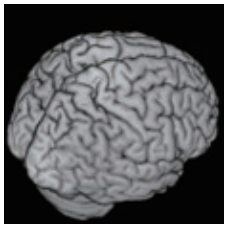


Shinji Kakei

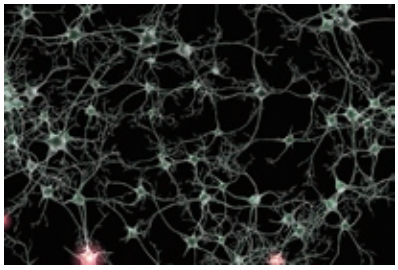
From neurons to motor control to brain disorders

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.



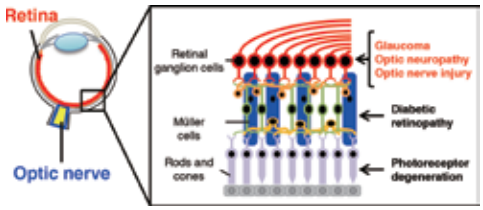
The brain is an assembly of neural networks.

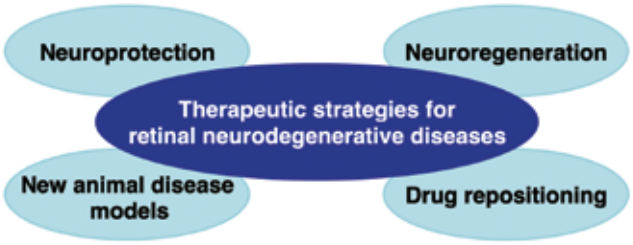


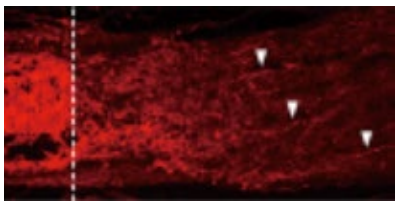
Visual Research Project

Elucidating the Pathology and Developing Therapeutic Strategies for Retinal Neurodegenerative Diseases

Takayuki Harada





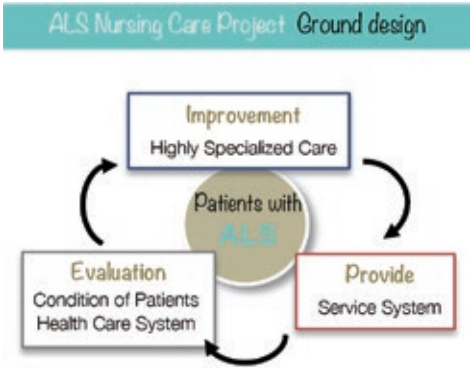


DOCK3 overexpression enhances optic nerve regeneration. Arrowheads indicate regenerating axons.
Namekata et al., *PNAS,* 2010.

ALS Nursing Care Project

Optimization of Nursing Care and Community Based Management for Incurable Diseases

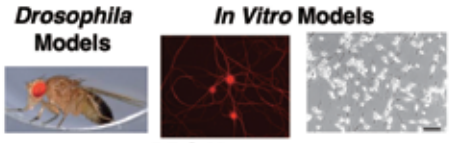
Yuki Nakayama

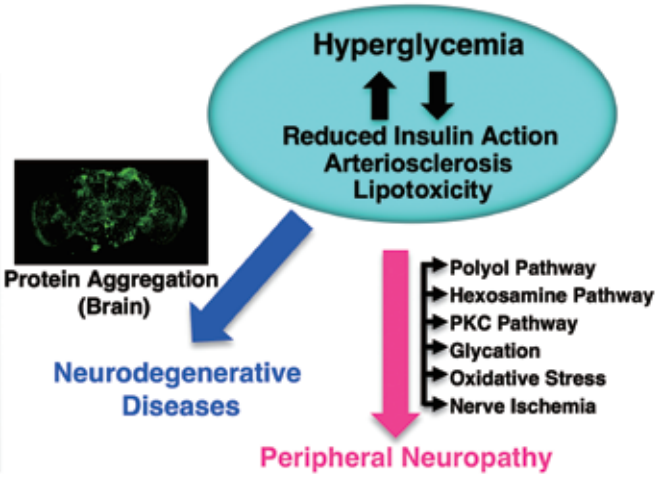


Diabetic Neuropathy Project

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

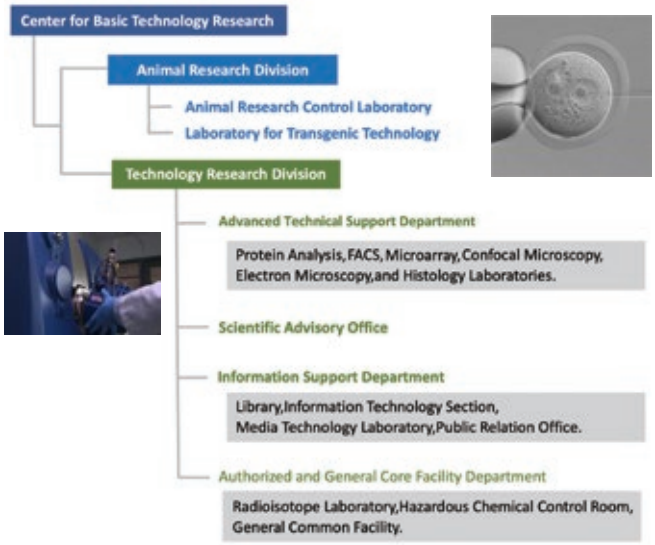
Kazunori Sango

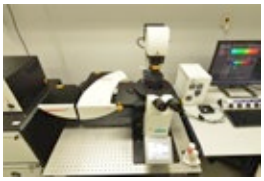




Center For Basic Technology Research

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.

Futoshi Shibasaki

at BIO-Europe

Translational Research Planning and Management Office

Translating the Fruits of Basic Research into the Seeds of Clinical Treatments

Masanari Itokawa

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.

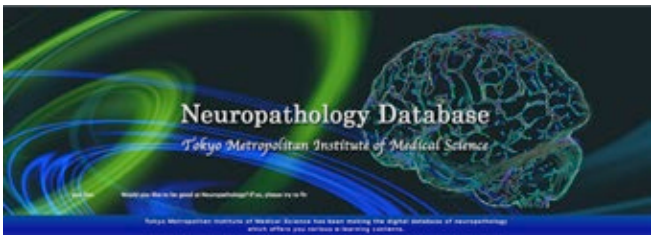
Many discoveries in science are made fortuitously, and it requires an open mind, free from bureaucratic obligations to see the importance and potential of these discoveries. We provide tools to determine whether findings from the bench can be developed into useful medical technology. Our work is akin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

Laboratory of Neuropathology

Slide Library and Digital Archive of Neuropathologies

Nobutaka Arai

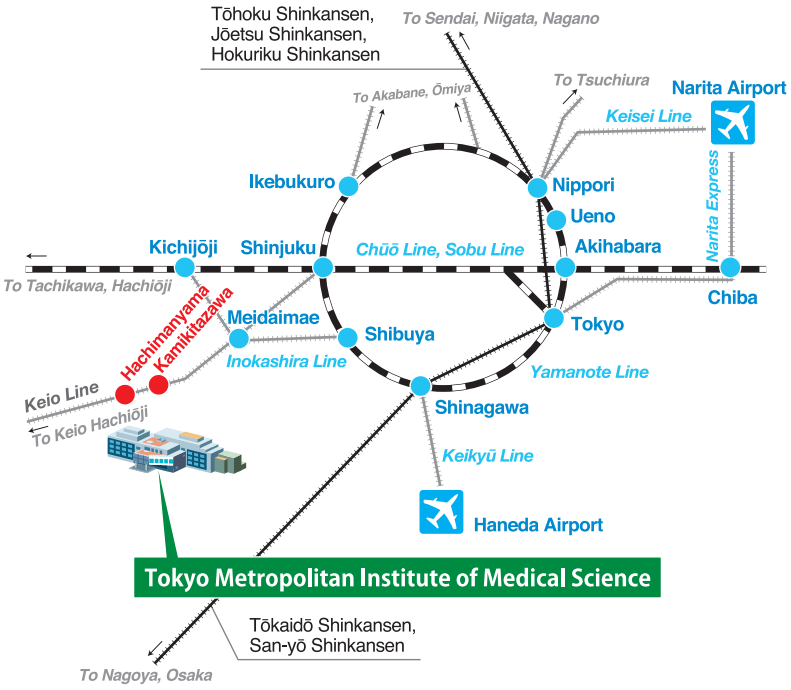
The laboratory of neuropathology has more than 5000 sets of slides generated from the autopsied brains of people with various neurological diseases. We have been scanning these slides using virtual slide instruments to generate composite digital slides of various neuropathologies.



https://pathologycenter.jp/english/en_index.html

Access Map

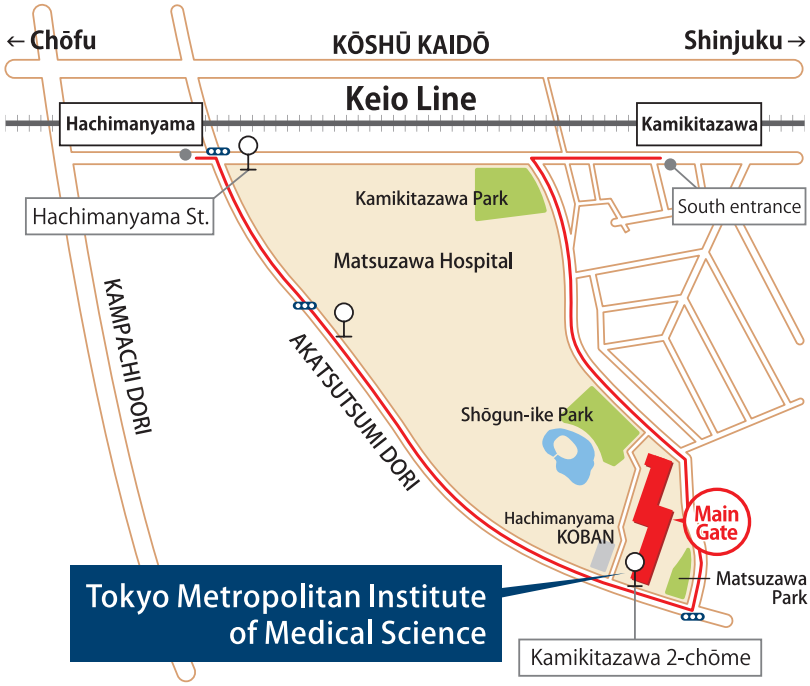
Tokyo Metropolitan Institute of Medical Science	
Address	2-1-6 Kamikitazawa, Setagaya-ku, Tokyo, 156-8506, Japan
Tel	+81-3-5316-3100
Fax	+81-3-5316-3150



AIRPORT to INSTITUTE

From Narita Airport to Kamikitazawa Station / Hachimanyama Station	
Narita Airport - Shinjuku Station	JR Narita Express
Shinjuku Station - 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 Station - 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**

Hachimanyama Station - Kamikitazawa 2-chōme	Keio bus / Odakyū bus
Kamikitazawa 2-chōme - Institute	Walk

http://www.igakuken.or.jp/english/

As of 2019