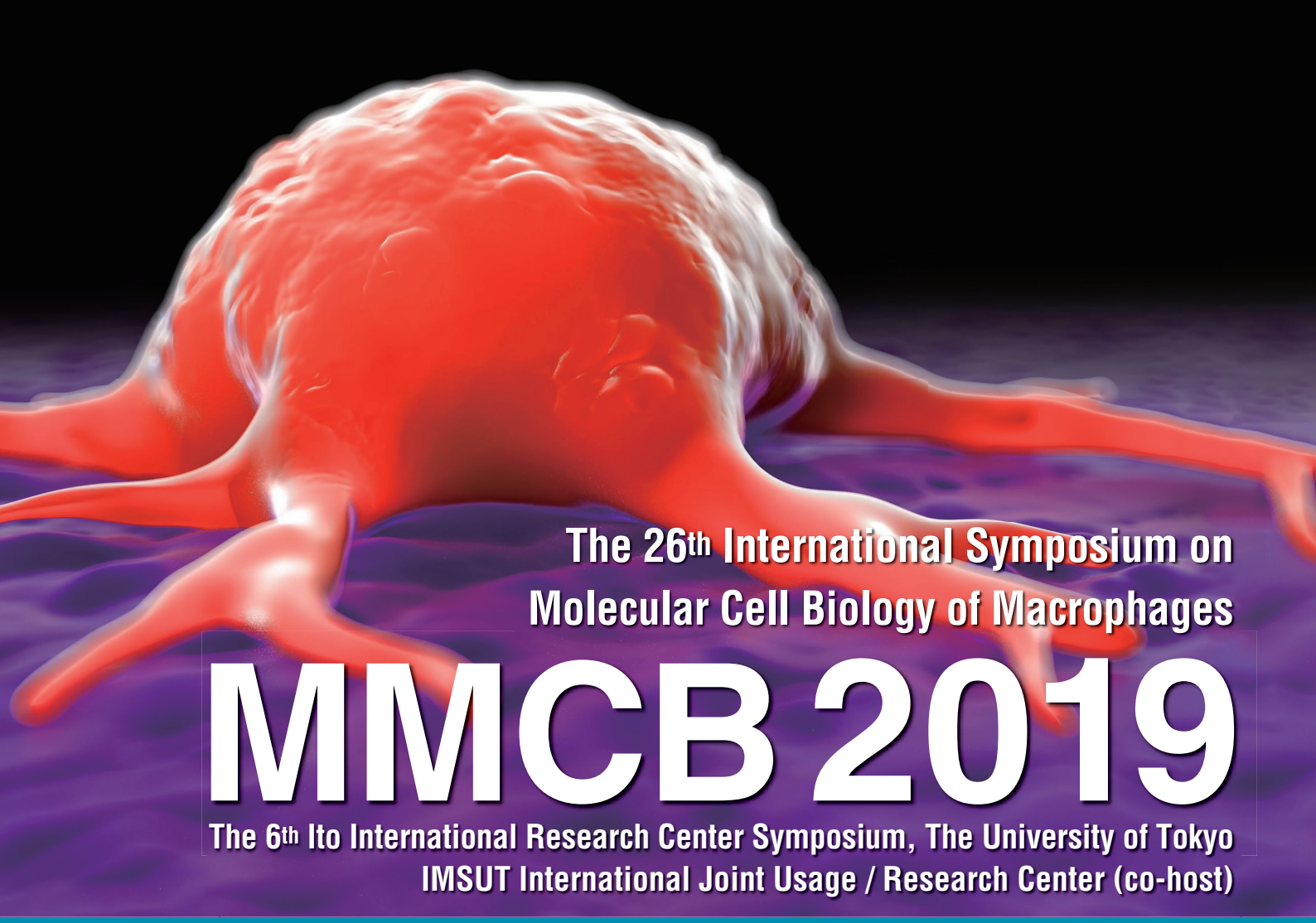
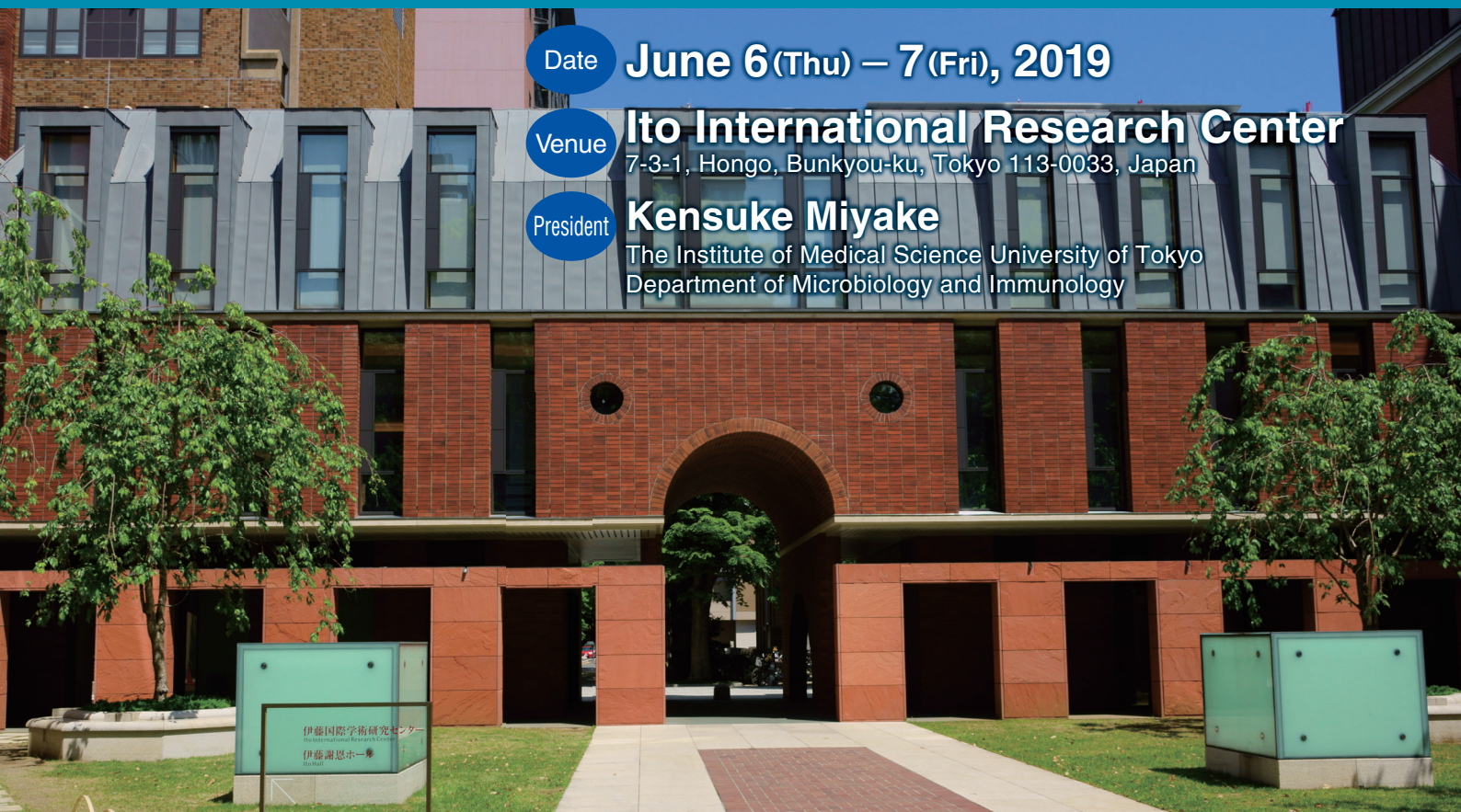


The 26th International Symposium on
Molecular Cell Biology of Macrophages

MMCB 2019

The 6th Ito International Research Center Symposium, The University of Tokyo
IMSUT International Joint Usage / Research Center (co-host)

Decoding and controlling inflammatory diseases



Date June 6 (Thu) – 7 (Fri), 2019

Venue Ito International Research Center
7-3-1, Hongo, Bunkyou-ku, Tokyo 113-0033, Japan

President Kensuke Miyake
The Institute of Medical Science University of Tokyo
Department of Microbiology and Immunology

MMCB2019

The 26th International Symposium on
Molecular Cell Biology of Macrophages

The 6th Ito International Research Center Symposium,The University of Tokyo
IMSUT International Joint Usage / Research Center (co-host)

Decoding and controlling inflammatory diseases

MMCB2019 Secretariat

c/o A & E Planning Co., Ltd.

Hitotsubashi Bekkan 4F, 2-4-4
Hitotsubashi, Chiyodaku, Tokyo 101-0003
Tel: +81-3-3230-2744 Fax: +81-3-3230-2479

Welcome to MMCB2019 in Tokyo

Kensuke Miyake
President of MMCB2019
Professor, University of Tokyo

On behalf of the organizing committee, it is my great pleasure to host the 26th International Symposium on Molecular Cell Biology of Macrophages (MMCB2019) on June 6th and 7th, 2019 at Ito International Research Center (IIRC) at the Hongo campus of the University of Tokyo.

In 1991, Professor Kouji Matsushima (Professor emeritus at The University of Tokyo) organized the 1st MMCB at Kanazawa and started the Japanese Society for Molecular Cell Biology of Macrophages. Since then, MMCB has been held annually. Two years ago, Professor Toshiaki Ohteki has become the 2nd President of Japanese Society for Molecular Cell Biology of Macrophages.

Inflammation, defined as “calor, dolor, rubor, and tumor”, occurs in a variety of diseases ranging from infectious diseases to autoimmune diseases. Recent progresses in our understanding of molecular and cellular mechanisms behind inflammation have expanded a pathogenic role of inflammation from the above mentioned “conventional” inflammatory diseases to metabolic diseases such as obesity and atherosclerosis, heart failure, ageing, carcinogenesis, and cancer metastasis. Monocytes/macrophages are a key player driving inflammation in the disease states. Our understanding of molecular mechanisms behind inflammatory diseases helps us to identify a therapeutic target, and enables us to control a variety of inflammatory diseases such as rheumatoid arthritis and psoriasis. This symposium, therefore, focuses on our continuous efforts “Decoding and controlling inflammatory diseases”.

The symposium consists of 4 sessions focusing on the relation between inflammation and diseases. The sessions consist of “Inflammatory disease”, “Cancer immunity”, “Tissue repair, fibrosis, and aging” and “Metabolism and macrophage”. Distinguished scientists are going to present their cutting-edge results. In addition to the symposia by invited speakers, we welcome all of you to poster session and selected oral presentation from posters.

We hope all of you, including young talented scientists and already established scientists, to enjoy state-of-the-art presentation and hot discussion.

General information

Theme

-Decoding and controlling inflammatory diseases-

Meeting Dates

June 6 (Thu), June 7 (Fri), 2019

Conference Venue

Ito International Research Center
7-3-1, Hongo, Bunkyou-ku, Tokyo 113-0033, Japan
URL: https://www.u-tokyo.ac.jp/adm/iirc/en/

Organizing Committee

President of MMCB: Toshiaki Ohteki, Tokyo Medical and Dental University
Conference Chair: Kensuke Miyake, The Institute of Medical Science, The University of Tokyo
Program Committee Members: Tsuneyasu Kaisho, Ichiro Manabe, Kensuke Miyake
Steering Committee Members: Ken Ishii, Masaru Ishii, Atsushi Kumanogoh,
Kouji Matsushima, Kiyoshi Takeda, Osamu Takeuchi, Masato Tanaka, Sho Yamasaki
Secretary-General: Ryutaro Fukui

Host

The Japanese Society for Molecular Cell Biology of Macrophages

Co-Host

IMSUT International Joint Usage / Research Center

Registration

Ito International Research Center
June 6 (Thu), 2019: Starts 9:00 a.m.
June 7 (Fri), 2019: Starts 9:00 a.m.

Social Event

Welcome Reception (Ito International Research Center)
June 6 (Thu), 2019: 18:45 - 20:45

Instructions for Chairpersons

Chairpersons are requested to be seated at the chair's desk on the stage no later than 5 minutes before starting the session.

Poster viewing with Lunch

We are pleased to offer you lunch boxes.
They will be handed out on the first-come-first-served basis.
Please note that we only have a limited number.

* On the second basement, participants can drink and eat in the Event Space and Ito Hall.

Instruction for Invited Speakers

Only computer-based PowerPoint slides will be accepted. Please bring your presentation slides in USB or your own laptop PC to the PC desk in Ito Hall no later than 30 minutes before your talk session begins. Due to tight schedule, you are requested to strictly keep to your time allocation.
Remaining time will be notified by the bell signals as follows;

Simposium 1, 2, 4, 5 (30 minutes per presentation (incl. Q & A))
1 ring: 10 minutes to the end of presentation
2 rings: 2 minutes to the end of presentation
3 rings: End of presentation

Simposium 3 (15 minutes per presentation (incl. Q & A))
1 ring: 5 minutes to the end of presentation
2 rings: 2 minutes to the end of presentation
3 rings: End of presentation

Instruction for Poster Presenters

Poster presentation and viewing
Ito International Research Center

Poster Discussion	: June 6 (Thu) 17:30 - 18:30
Poster Award Ceremony	: June 7 (Fri) 16:00 - 16:15
Poster Size (maximum)	: W900mm × H1200mm, must be printed in English
Poster No.	: Provided by the secretariat

* We will provide the poster numbers only. Please prepare the title of your poster by yourself.

Set up	: June 6 (Thu) 9:00 - 12:00
Removal	: June 7 (Fri) 15:00 - 17:00

Any poster left on the panel after the removal time will be discarded by the secretariat.

Acknowledgement for Sponsorship（2019年5月24日現在）

The organizing committee of MMCB2019 gratefully acknowledges the generous financial support of the following organizations.

GRANTS（助成金）

SECOM Science and Technology Foundation（公益財団法人 セコム科学技術振興財団）

Inoue Foundation for Science（公益財団法人 井上科学振興財団）

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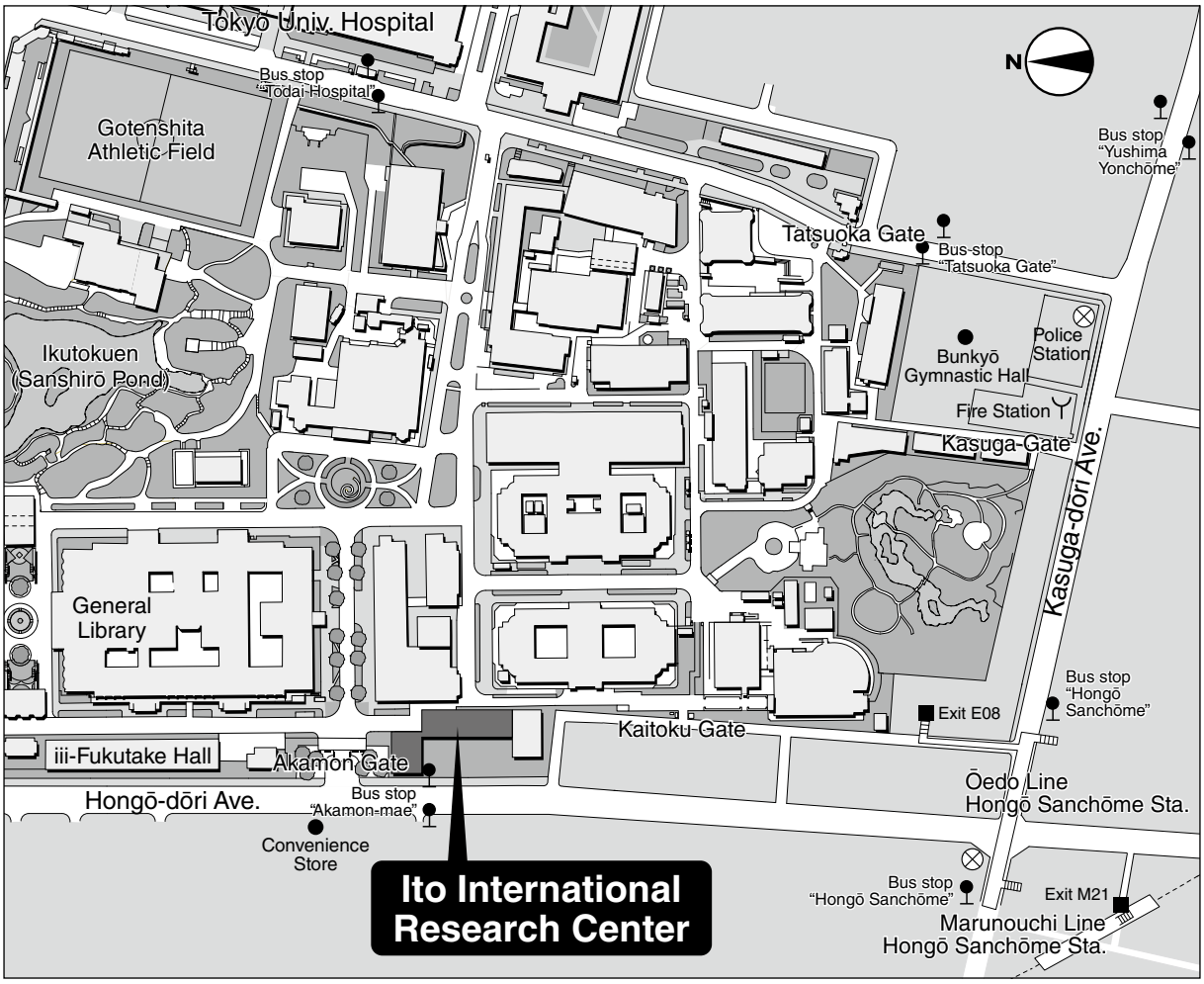
YOUNG INVESTIGATOR AWARDS（若手研究奨励賞）

BioLegend, Inc.（BioLegend Japan 株式会社）

Access Map

Ito International Research Center

7-3-1, Hongo, Bunkyou-ku, Tokyo 113-0033
TEL:+81-3-5841-0779 (AM9:00-PM5:30, Weekdays only)



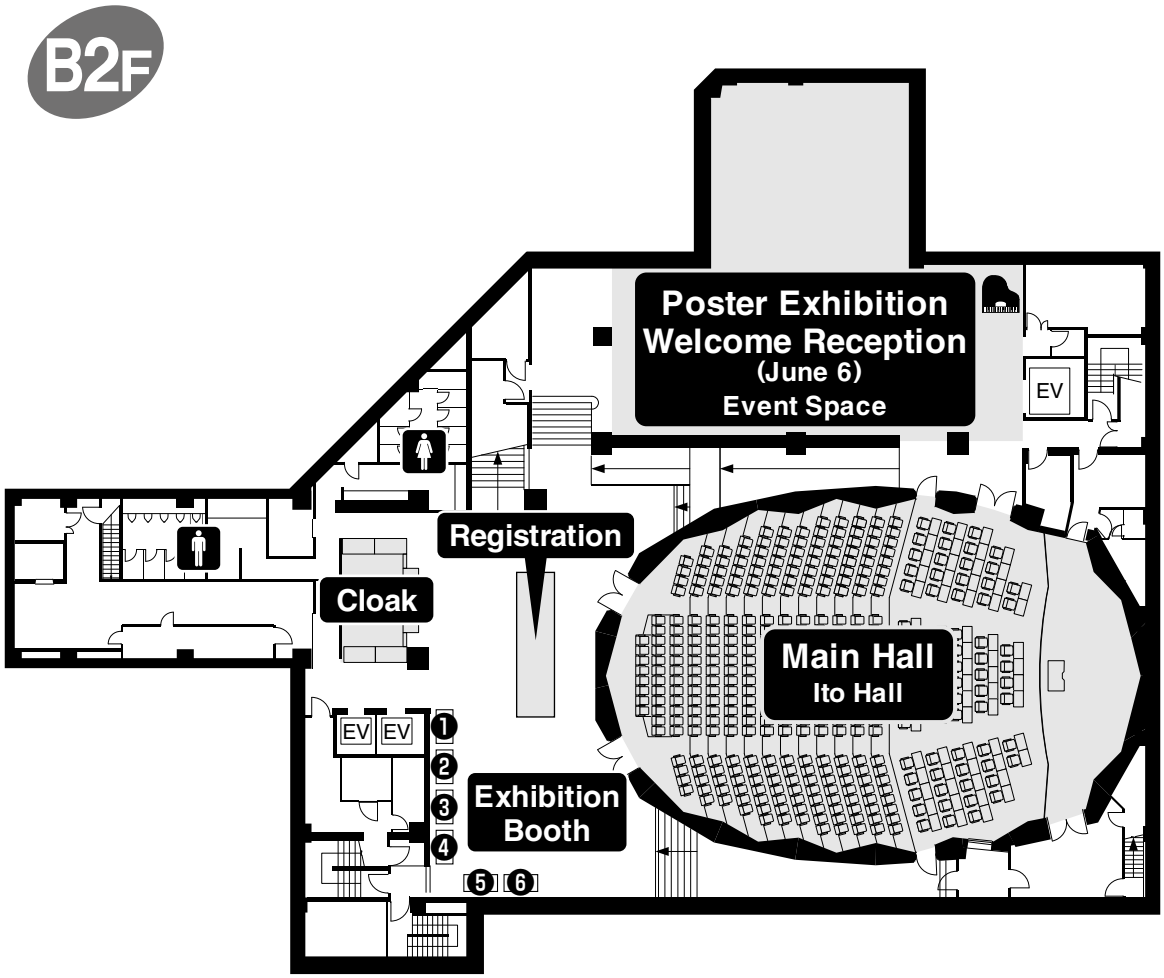
Access by train and bus

Nearest station (Subway)	Time required
Hongo-sanchome (Marunouchi Line)	8 minutes' walk
Hongo-sanchome (Oedo Line)	6 minutes' walk
Kasuga (Mita Line)	10 minutes' walk

Korakuen Station (Marunouchi-Line)	[Subway]	Subway Marunouchi-Line (for Ogikubo) ➡ get off at Hongo-sanchome Station.
Ochanomizu Station (JR Chuo-Line, JR Sobu-Line)	[Subway]	Subway Marunouchi-Line (for Ikebukuro) ➡ get off at Hongo-sanchome Station.
	[Subway]	Subway Chiyoda-Line (for Toride) ➡ get off Yushima Station or Nezu Station.
	[Toei Bus]	茶51 for Komagome Station South Exit or 東43 for Arakawa-dote-soshajo ➡ get off at Todai-Akamon-Mae, Todai-Seimon-Mae, Todai-Nogakubu-Mae stops.
	[Toei Bus]	学07 for The University of Tokyo ➡ get off at Tatsuokamon, Todai-Byoin-Mae, Todai-Konai stops.
Okachimachi (JR Yamanote-Line, other lines)	[Toei Bus]	都02 for Otsuka Station or 上69 Otakibashi-shako-mae ➡ get off Hongo-sanchome Eki-mae stop.
		都02 for Otsuka Station or 上69 Otakibashi-shako-mae ➡ get off Yushima-yonchome stop.
Ueno (JR Yamanote-Line, other lines)	[Toei Bus]	学01 for The University of Tokyo ➡ get off at Tatsuokamon, Todai-Byoin-Mae, Todai-Konai stops.

Venue Map

Ito International Research Center



Exhibition Booth

1. Katayama Chemical Industries Co., Ltd.
2. TOMY DIGITAL BIOLOGY CO., LTD.
3. Bio-Rad Laboratories K.K.
4. InvivoGen Limited
5. Fluidigm K.K.
6. SHIMADZU CORPORATION

Program

June 6 (Thu)

9:00- **Registration**

9:30-9:35 **Opening Remarks: Kensuke Miyake** (Chairman of MMCB2019)

9:35-12:05 **Symposium 1: Inflammatory disease**

Chairpersons: **Tsuneyasu Kaisho** (Wakayama Medical University, Japan)
Kensuke Miyake (The University of Tokyo, Japan)

9:35-10:05 **S1-1** **Defective innate and adaptive immunity in mutant mice carrying a novel heterozygous missense mutation of a proteasome subunit, PSMB9, in a patient with autoinflammation and immunodeficiency**
Tsuneyasu Kaisho (Wakayama Medical University, Japan)

10:05-10:35 **S1-2** **Mechanisms controlling innate immune responses to nucleic acids**
Kensuke Miyake (The University of Tokyo, Japan)

10:35-11:05 **S1-3** **Cytosolic RNA sensing and inflammation**
Sun Hur (Harvard Medical School, USA)

11:05-11:35 **S1-4** **Tissue-Resident Innate Immune Responses during Obesity**
Timothy E. O'Sullivan (UCLA, USA)

11:35-12:05 **S1-5** **Reciprocal interaction between blood vessels and immune cells in CNS development**
Yoshiaki Kubota (Keio University, Japan)

12:15-13:15 **Poster viewing with Lunch 1**

13:30-16:00 **Symposium 2: Cancer Immunity**

Chairpersons: **Shin-ichiro Fujii** (RIKEN, Japan)
Ken J. Ishii (The University of Tokyo, Japan)

13:30-14:00 **S2-1** **Anti-diabetes drug, metformin, drives metabolic reprogramming in tumor microenvironment, leading to manifestation of anti-tumor immunity**
Heiichiro Udono (Okayama University, Japan)

14:00-14:30 **S2-2** **Development of therapeutic cancer vaccine utilizing invariant NKT cell-licensed dendritic cells**
Shin-ichiro Fujii (RIKEN, Japan)

Symposium 1:
Inflammatory disease

Chairpersons: **Tsuneyasu Kaisho** (Wakayama Medical University, Japan)
Kensuke Miyake (The University of Tokyo, Japan)

Speakers: **Tsuneyasu Kaisho** (Wakayama Medical University, Japan)
Kensuke Miyake (The University of Tokyo, Japan)
Sun Hur (Harvard Medical School, USA)
Timothy E. O'Sullivan (UCLA, USA)
Yoshiaki Kubota (Keio University, Japan)

S1-1 Defective innate and adaptive immunity in mutant mice carrying a novel heterozygous missense mutation of a proteasome subunit, PSMB9, in a patient with autoinflammation and immunodeficiency

Tsuneyasu Kaisho[1)], Hiroaki Hemmi[1)], Nobuo Kanazawa[2)]

1) Department of Immunology, Institute of Advanced Medicine, Wakayama Medical University
2) Department of Dermatology, Wakayama Medical University

Key Words: autoinflammatory disease, immunodeficiency, proteasome

Autoinflammatory diseases are monogenic diseases manifesting inflammatory conditions due to dysregulated innate immunity. Homozygous, compound heterozygous or digenic loss-of-function mutations in genes of various proteasome subunits cause a group of autoinflammatory diseases, termed proteasome-associated autoinflammatory syndromes (PRAAS). The first PRAAS was reported by Nakajo in 1939 and Nishimura in 1950 and named as Nakajo-Nishimura syndrome (NNS), which was found to be caused by missense homozygous mutation in *PSMB8* gene encoding a proteasome subunit, β5i, with protease activity.

The proteasome is a protein complex involved in intracellular protein homeostasis by degrading unnecessary or useless proteins after their ubiquitination. There are three types of proteasomes, i.e. constitutive proteasome, immunoproteasome and thymoproteasome, which carry β1/β2/β5, β1i/β2i/β5i, and β1i/β2i/β5t as subunits bearing protease activity, respectively. The latter two proteasomes are also involved in generation of MHC class I-restricted antigen peptides. In PRAAS, proteasome activity is severely impaired and ubiquitin is accumulated. Some reports say that proinflammatory cytokines such as IL-6 or type I IFNs are overproduced in PRAAS, but this dysregulation cannot fully account for pathogenesis of PRAAS. Furthermore, although mutant mice lacking either or some of proteasome subunits show dysfunction or decrease of CD8 T cells, such CD8 T cell defects have not been reported in PRAAS. Thus, it still remains largely unknown how the proteasome defect leads to autoinflammatory diseases.

We have found a patient with manifestations similar to, but distinct from NNS. The patient did not have a mutation in *PSMB8* gene, but had a novel, de novo, missense and heterozygous mutation in *PSMB9* gene encoding β1i. We have then generated the mice carrying the mutation and found that both innate and adaptive immune cells were affected in the heterozygous *PSMB9* mutant mice. The phenotypes were not identical to, but overlapping with the patient manifestations. Noteworthy, in both the patient and heterozygous mutant mice, proteasome maturation was impaired, but ubiquitin accumulation was not so prominent. These results prompt us to propose a novel category of autoinflammatory diseases, which can be called as “proteasome-associated autoinflammation and immunodeficiency disease (PRAID)”.

BIOGRAPHY

Name: Tsuneyasu Kaisho

Position: Professor

Affiliation: Department of Immunology, Institute of Advanced Medicine, Wakayama Medical University

E-mail: tkaisho@wakayama-med.ac.jp

Education and Appointments:

[Education]

1978-1984	Osaka University, School of Medicine, obtained M.D. in 1984
1986-1990	Osaka University, Graduate School of Medicine, obtained Ph.D. in 1990

[Research Appointment]

1984-1986	Physician, Osaka University Hospital and National Osaka-Minami Hospital, Osaka, Japan
1990-1994	Research Associate, Osaka University Medical School, Osaka, Japan
1994-1997	Postdoctoral fellow, Genetic Institute, University of Cologne, Cologne, Germany.
1997-1999	Research Associate, Hyogo College of Medicine, Hyogo, Japan
1999-2004	Associate Professor, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan
2002-2011	Team Leader, Laboratory for Host Defense, RIKEN Research Center for Allergy and Immunology, Kanagawa, Japan
2011-2014	Professor, Laboratory for Immune Regulation, World Premier International Immunology Frontier Research Center, Osaka University, Osaka, Japan
2014-present	Professor, Department of Immunology, Institute of Advanced Medicine, Wakayama Medical University

Specialty and Research Field of Interest:

Clarifying the molecular and cellular mechanisms for immune homeostasis and its dysregulation, in which dendritic cells or macrophages are mainly involved.

Selected publication:

1. K. Hoshino, et al. IκB kinase-α is critical for interferon-α production induced by Toll-like receptors 7 and 9. Nature 440: 949-953, 2006.
2. I. Sasaki, et al. Spi-B is critical for plasmacytoid dendritic cell function and development. Blood 120:4733-4743, 2012.
3. C. Yamazaki, et al. Critical roles of a dendritic cell subset expressing a chemokine receptor, XCR1. J. Immunol. 190:6071-6082, 2013.
4. T. Ohta, et al. Crucial roles of XCR1-expressing dendritic cells and the XCR1-XCL1 chemokine axis in intestinal immune homeostasis. Sci. Rep. Mar 23;6:23505, 2016.
5. T. Orimo, et al. Cholera toxin B induces interleukine-1β production from resident peritoneal macrophages through pyrin as well as NLRP3 inflammasome. Int Immunol, early online.

Symposium 2:
Cancer Immunity

Chairpersons: **Shin-ichiro Fujii** (RIKEN, Japan)
Ken J. Ishii (The University of Tokyo, Japan)

Speakers: **Heiichiro Udono** (Okayama University, Japan)
Shin-ichiro Fujii (RIKEN, Japan)
Ken J. Ishii (The University of Tokyo, Japan)
Caetano Reis e Sousa (The Francis Crick Institute, UK)
Irving L. Weissman (Stanford University, USA)

S2-1 Anti-diabetes drug, metformin, drives metabolic reprogramming in tumor microenvironment, leading to manifestation of anti-tumor immunity

Heiichiro Udono[1)], Mikako Nishida[1)], Takenori Uehara[2)]

1) Department of Immunology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
2) Department of Orthopedic Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

Key Words: Tumor microenvironment, Immuno-Metabolism, TILs, MDSCs, TAMs

Metformin (Met) is the most widely used drug in the world as a first choice for treatment of patients with type 2 diabetes (T2DM). Intriguingly, Met is known to reduce the rates of cancer incidence and mortality of patients with T2DM, comparing with those taking other drugs. Using mice tumor models, we previously demonstrated the anti-tumor effect of Met is mediated by $CD8^+$ tumor infiltrating T lymphocytes (TILs), as the effects was canceled in T cell deficient mice and in WT mice depleted of $CD8^+$T cells in vivo. Met confers synergistic effect with anti-PD-1 Ab, thus, better tumor inhibitory effect than either mono-therapy alone, through induction of vigorous proliferation of CD8TILs that can secrete multiple cytokines. The action of Met on CD8TILs seems to be mediated by reactive oxygen species (ROS), since in vivo elimination of ROS by N-acetyl Cysteine (NAC) or GSH, completely abrogates the effect. Met-induced mitochondrial ROS elevates glycolysis in CD8TILs, whereas down-regulates that of tumor cells. This indicates that Met improves metabolic imbalance between CD8TILs and tumor cells, until otherwise tumor cells dominate immune cells by taking large amount of glucose.

The above mentioned metabolic change is also appreciated in regulatory T cells (Treg) and $CD11b^+$ cells including myeloid-derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs). With Met administration, metabolic change from oxidative phosphorylation (OxPhos) to glycolysis is evident in TAMs, which skews phenotypic change of TAMs from M2-to M1-like macrophages, resulting in growth inhibition of certain tumors even in T cell deficient mice. We will discuss how Met affects metabolic states in immune cells by which apparent inhibition of tumor growth is achieved in vivo.

BIOGRAPHY

Name: Heiichiro Udono

Position: Professor

Affiliation: Department of Immunology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences

E-mail: udono@cc.okayama-u.ac.jp

Education and Appointments:

March 1985:	Graduation from Nagasaki University School of Medicine.
March 1990:	Graduation from Nagasaki University Graduate School of Medicine.
June 1991 - September 1993:	Postdoc., The Mount Sinai Medical Center, New York, USA.
October 1993 - December 1997:	Assistant Professor, Okayama University School of Medicine.
January 1998 - December 1998:	Lecturer, Nagasaki University School of Medicine.
January 1999 - March 2004:	Associate Professor, Nagasaki University School of Medicine.
March 2003 - March 2011:	Team Leader, RIKEN, Japan.
April 2011 - at present:	Professor, Department of Immunology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan.

Specialty and Research Field of Interest:

Immunology, Immuno-metabolism in anti-tumor immunity

Selected publication:

1. Metformin induces CD11b^{+} cell-mediated growth inhibition of an osteosarcoma: implications for metabolic reprogramming of myeloid cells and antitumor effects.
   Int. Immunology 2019 in press.
2. Metformin Promotes the Protection of Mice Infected with Plasmodium yoelii Independently of γδ T Cell Expansion. Frontiers in Immunology, 2018 Dec 13; 9: 2942.
3. Attenuation of CD4^{+}CD25^{+}regulatory T cells in the tumor microenvironment by metformin, a type 2 diabetes drug. eBioMedicine (published by The Lancet), 25,154-64, 2017.
4. Immune-mediated anti-tumor effect by type 2 diabetes drug, metformin. PNAS 112(6):1809-14, 2015.

Symposium 3:
Selected titles from poster presentation

Chairpersons: **Toshiaki Ohteki** (Tokyo Medical and Dental University, Japan)

Speakers: **Koutarou Nakamura** (Tokyo Metropolitan Institute of Medical Science, Japan)
Naoki Morita (The University of Tokyo, Japan)
YeeKien Chong (Kyoto University, Japan)
Tetsuro Kobayashi (RIKEN, Japan / NIH, USA)

16:15-17:15 **Symposium 3: Selected titles from poster presentation**

Chairpersons: **Toshiaki Ohteki** (Tokyo Medical and Dental University, Japan)

*Refer to the abstract of poster session

16:15-16:30 **S3-1** (P-03*)
DJ-1 is a novel damage-associated molecular pattern in ischemic stroke
Koutarou Nakamura (Tokyo Metropolitan Institute of Medical Science, Japan)

16:30-16:45 **S3-2** (P-21*)
GPR31-dependent dendrite protrusion of intestinal CX_3CR1^+ cells by bacterial metabolites
Naoki Morita (The University of Tokyo, Japan)

16:45-17:00 **S3-3** (P-23*)
The roles of CyclinJ in macrophages in tuning immune homeostasis
YeeKien Chong (Kyoto University, Japan)

17:00-17:15 **S3-4** (P-35)
Innate lymphoid cells regulate microbiome balance by tuning epithelial barrier
Tetsuro Kobayashi (RIKEN, Japan / NIH, USA)

Symposium 4:
Tissue repair, fibrosis, and aging

Chairpersons: **Kazuyo Moro** (Osaka University, Japan / RIKEN, Japan)
Hiroki Tanaka (Osaka University, Japan)

Speakers: **Hiroki Tanaka** (Osaka University, Japan)
Eiji Hara (Osaka University, Japan)
Kazuyo Moro (Osaka University, Japan / RIKEN, Japan)
Masanori Aikawa (Harvard Medical School, USA)
Steffen Jung (Weismann Institute of Science, Israel)

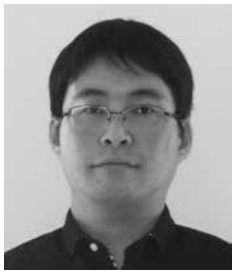
S4-1 Regnase-1: A Key regulator of the mRNA stabilization during interleukin-17-induced inflammation

Hiroki Tanaka
Immunology Frontier Research Center (IFReC), Osaka University

Key Words: mRNA stability, Regnase-1, Interleukin-17, phosphorylation, subcellular localization

Regnase-1, a member of the CCCH zinc finger protein family, is an endoribonuclease that regulates inflammation-associated gene expression. Regnase-1 is induced in response to inflammatory stimuli, such as TLR ligands or proinflammatory cytokines, and degrades inflammation-associated mRNAs, thereby forming a negative feedback circuit to diminish excess inflammatory response. This is confirmed by studies using Regnase-1 deficient mice, which showed severe autoimmune and inflammatory phenotypes. On the other hand, Regnase-1 is inactivated by its phosphorylation and degradation in MyD88-dependent pathways or by its degradation by MALT1 protease in TCR signaling, raising the possibility that Regnase-1 function is controlled by its post-translational processes. We recently found a novel inactivation mechanism of Regnase-1 via its phosphorylation by proinflammatory cytokine IL-17. IL-17 stimulation induces Regnase-1 phosphorylation in non-hematopoietic cells but not in hematopoietic cells. This phosphorylation leads to a change in subcellular localization of Regnase-1, (from the ER to the cytosols), to attenuate the RNA decay ability of Regnase-1 independent of protein degradation. We constructed knockin mice in which the phosphorylation sites of Regnase-1 was completely blocked. They were highly resistant to IL-17-mediated inflammation under *in vitro* and *in vivo* conditions. These results suggest that Regnase-1 phosphorylation causes an apparent loss of the inhibitory control of mRNA expression and that is important for fine-tuning of the expression level of IL-17-associated inflammatory genes.

BIOGRAPHY



Name: Hiroki Tanaka

Position: Assistant professor

Affiliation: Immunology Frontier Research Center (IFReC), Osaka University

E-mail: htanaka@ifrec.osaka-u.ac.jp

Education and Appointments:

Ph.D. Osaka University

Specialty and Research Field of Interest:

Biochemistry and molecular biology of host innate immunity and inflammation.

Selected publication:

1. Nagahama Y et al. Regnase-1controls colon epithelial regeneration via regulation of mTOR and purine metabolism. *PNAS U.S.A*. 115 11036-11041 (2018)
2. Tanaka H et al. Phosphorylation-dependent Regnase-1 release from endoplasmic reticulum is critical in IL-17 response. *J. Exp. Med*. *In Press*

Symposium 5:
Metabolism and Macrophage

Chairpersons: **Ichiro Manabe** (Chiba University, Japan)
Atsushi Kumanogoh (Osaka University, Japan)

Speakers: **Ichiro Manabe** (Chiba University, Japan)
Eicke Latz (University of Bonn, Germany)
Ajay Chawla (University of California, USA)
Yumiko Oishi (Nippon Medical School, Japan)
Atsushi Kumanogoh (Osaka University, Japan)

S5-1 Macrophages in cardiac physiology and disease

Ichiro Manabe

Department of Disease Biology and Molecular Medicine, Chiba University Graduate School of Medicine

Key Words: heart failure, arrhythmia, metabolism

Heart failure is a complex clinical syndrome characterized by cardiac function that is insufficient to meet systemic demand. The prevalence of heart failure is rapidly increasing partly due to the aging of society so that heart failure is now considered as a global pandemic. While heart failure involves cardiac dysfunction, its development and consequences are greatly affected by various comorbidities. For instance, nearly half of chronic heart failure patients also have chronic kidney disease, which increases their rate of cardiovascular mortality, suggesting cardiorenal linkage via mechanisms still poorly understood. Moreover, within the heart various non-myocytes in addition to cardiomyocytes also crucially contribute to maintenance of homeostasis and pathologies. We and other have shown that macrophages play important roles in the inter-organ crosstalk as well as the intercellular interaction in the heart. We previously showed that cardiac macrophages are regulated by the heart-brain-kidney organ network and play a key role in cardiac adaptive response to pressure overload. Pressure overload in the heart activates renal collecting duct (CD) epithelial cells via sympathetic nerves. Within the kidneys, activated communication between CD cells, tissue macrophages and endothelial cells leads to secretion of CSF2, which in turn stimulates cardiac-resident Ly6C^{lo} macrophages essential for the myocardial adaptive response to pressure overload. We show that CD-specific deletion of the transcription factor *Klf5*, renal sympathetic denervation or adrenergic beta2 receptor blockade/deletion disrupts the renal response to cardiac pressure overload. Our results clearly demonstrate that dynamic interplay between the heart, brain and kidneys is necessary for proper adaptation to cardiac stress. We further found that Ly6C^{lo} macrophages contribute to the maintenance of homeostatic in the heart. For example, macrophages control cardiac metabolism in the steady state. Cardiac macrophages are also essential for maintenance of electrical conduction.

BIOGRAPHY

Name: Ichiro Manabe

Position: Professor

Affiliation: Department of Disease Biology and Molecular Medicine,
Graduate School of Medicine, Chiba University

E-mail: manabe-tky@umin.ac.jp

Education and Appointments:

1984-1990	M.D., Tottori University
1990-1994	Ph.D., Tottori University
1997-2001	Postdoctoral Fellow, Vascular Biology, University of Virginia
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2009-2012	Project Associate Professor, Global Center of Education and Research for Chemical Biology of the Diseases, The University of Tokyo
2012-2015	Lecturer, Department of Cardiovascular Medicine, Graduate School of Medicine, The University of Tokyo
2016-present	Professor, Chiba University

Specialty and Research Field of Interest:

Tissue macrophage functions and their regulatory mechanisms in non-communicable diseases.

Selected publication:

1. Fujiu K, Shibata M, Nakayama Y, Ogata F, Matsumoto S, Noshita K, Iwami S, Nakae S, Komuro I, Nagai R, *Manabe I. A heart-brain-kidney network controls adaptation to cardiac stress through tissue macrophage activation and cellular communication. ***Nat Med*** 23:611-622, 2017.
2. Oishi Y, Hayashi S, Isagawa T, Oshima M, Iwama A, Shimba S, Okamura H, *Manabe I. Bmal1 regulates inflammatory responses in macrophages by modulating enhancer RNA transcription. ***Sci Rep*** 7:7086, 2017.
3. Ogata F, Fujiu K, Matsumoto S, Nakayama Y, Shibata M, Oike Y, Koshima I, Watabe T, Nagai R, *Manabe I. Excess Lymphangiogenesis Cooperatively Induced by Macrophages and CD4+ T Cells Drives the Pathogenesis of Lymphedema. ***J Invest Dermatol*** 136:706-714, 2016.
4. Nishimura S, *Manabe I, Takaki S, Nagasaki M, Otsu M, Yamashita H, Sugita J, Yoshimura K, Eto K, Komuro I, Kadowaki T, Nagai R. Adipose natural regulatory B cells negatively control adipose tissue inflammation. ***Cell Metab*** 18:759-766, 2013.
5. Eguchi K, *Manabe I, Oishi-Tanaka Y, Ohsugi M, Kono N, Ogata F, Yagi N, Ohto U, Kimoto M, Miyake K, Tobe K, Arai H, Kadowaki T, Nagai R. Saturated Fatty Acid and TLR Signaling Link β Cell Dysfunction and Islet Inflammation. ***Cell Metab*** 15:518-533, 2012.

Poster Presentation & Poster Viewing

P-01* Functional neutralization of anti-IFN-γ auto-antibody in IFN-γ immune-surveillance

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Interferon (IFN)-γ confers crucial immune surveillance positively for immunomodulation (such as macrophage activation, antigen presentation, and T cell differentiation), antimicrobial (such as antiviral replication, microbial killing, and Major Histocompatibility Complex (MHC) induction), and anticancer activity (such as growth inhibition, cytotoxicity, and immune priming). Patients with adult-onset immunodeficiency, negative in Human Immunodeficiency Virus (HIV) infection, show defects in IFN-γ signaling and immune surveillance against mycobacterial infection. In addition to genetic defects, the presence of neutralizing anti-IFN-γ autoantibody (autoAb) is speculated. In the first part, detection of anti-IFN-γ autoAb and characterization of its neutralizing activity were carried out. First, Enzyme-linked Immunosorbent Assay (ELISA)-based colorimetric assays and immunoblotting was utilized for detecting autoAbs. Antibody-antigen reactivity and epitope clarification showed different patterns among these patients. Results showed the blockade of IFN-γ-activated Signal Transducer and activator of transcription (STAT)-1 activation and Interferon Regulatory Factor (IRF1) transactivation by patient serum containing autoAbs. Furthermore, IFN-γ-regulated inflammation, chemokine production, and cytokine production after T cell activation were also blocked. These results provide potential methods for detecting anti-IFN-γ autoAb and for characterizing the blockade effects of autoAbs on IFN-γ signaling and bioactivity. For the second part, the blockade effect of that antibody on IFN-γ-regulated antimicrobial activity will be detected. We will perform a model of monocyte-derived type 1 macrophage by using Phorbol-12-myristate-13-acetate (PMA) and IFN-γ induction. Furthermore, blockade effect of type 1 macrophage differentiation and bacterial phagocytosis/killing by anti-IFN-γ autoAbs will be performed by detection of inhibition on cell marker expression, attachment/engulfment phase, and Reactive Oxygen Species (ROS)/ Nitric oxide (NO) production. Those results will provide evidence of blockade effects of IFN-γ against antimicrobial activity by anti-IFN-γ autoAbs.

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