MMCB 2016

The 24th International Symposium on Molecular Cell Biology of Macrophages

Mononuclear Phagocyte in Homeostasis and Disease

Date June 4 (Sat) – 5 (Sun), 2016

Venue Sola City Conference Center
Ochanomizu sola city
4-6 Kandasurugadai, Chiyoda-ku, Tokyo 101-0062, Japan

President Toshiaki Ohteki
Tokyo Medical and Dental University

MMCB 2016

The 24th International Symposium on
Molecular Cell Biology of Macrophages

Mononuclear Phagocyte in Homeostasis and Disease

SECRETARIAT

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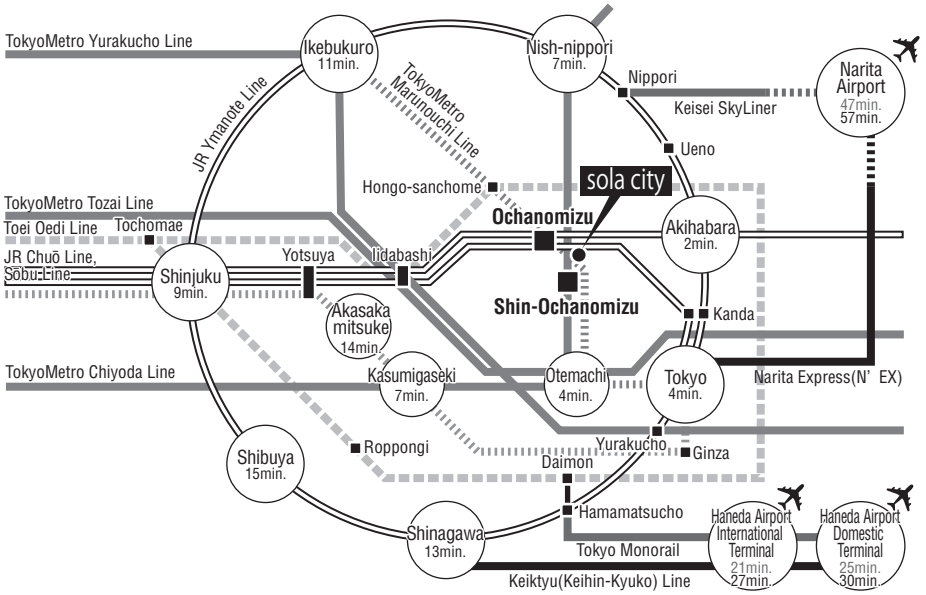
Access Map



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TolyoMetro Marunouchi Line: Ochanomizu Station
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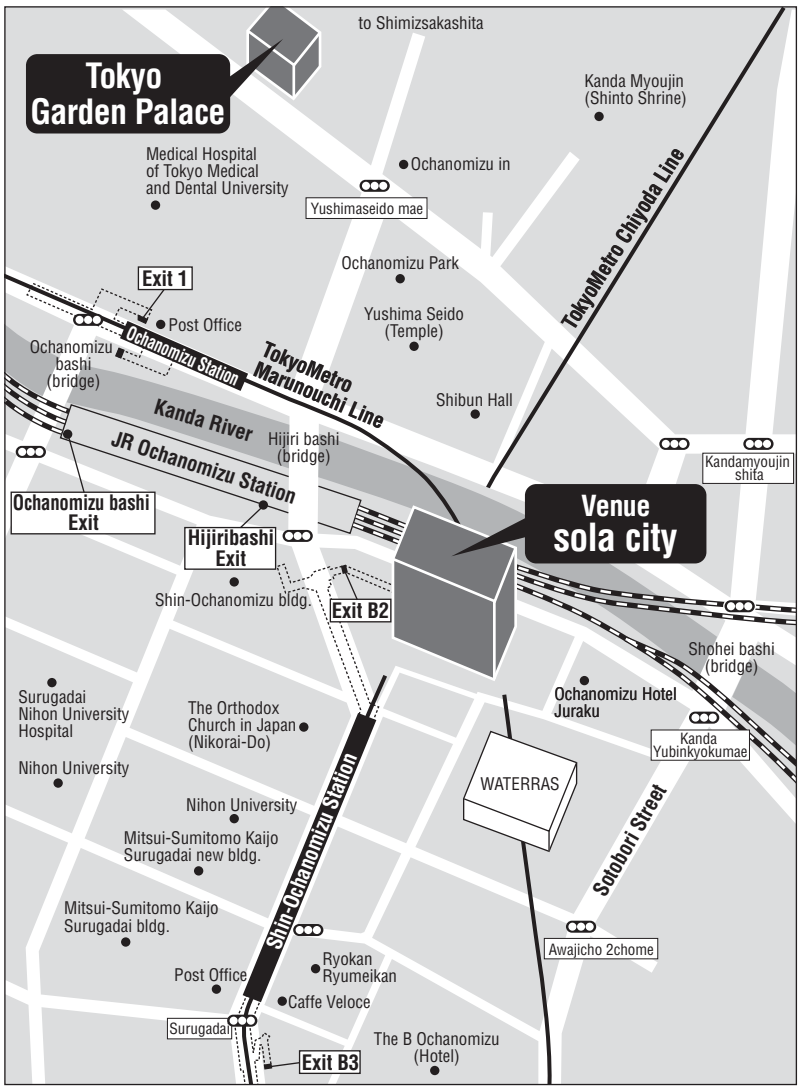
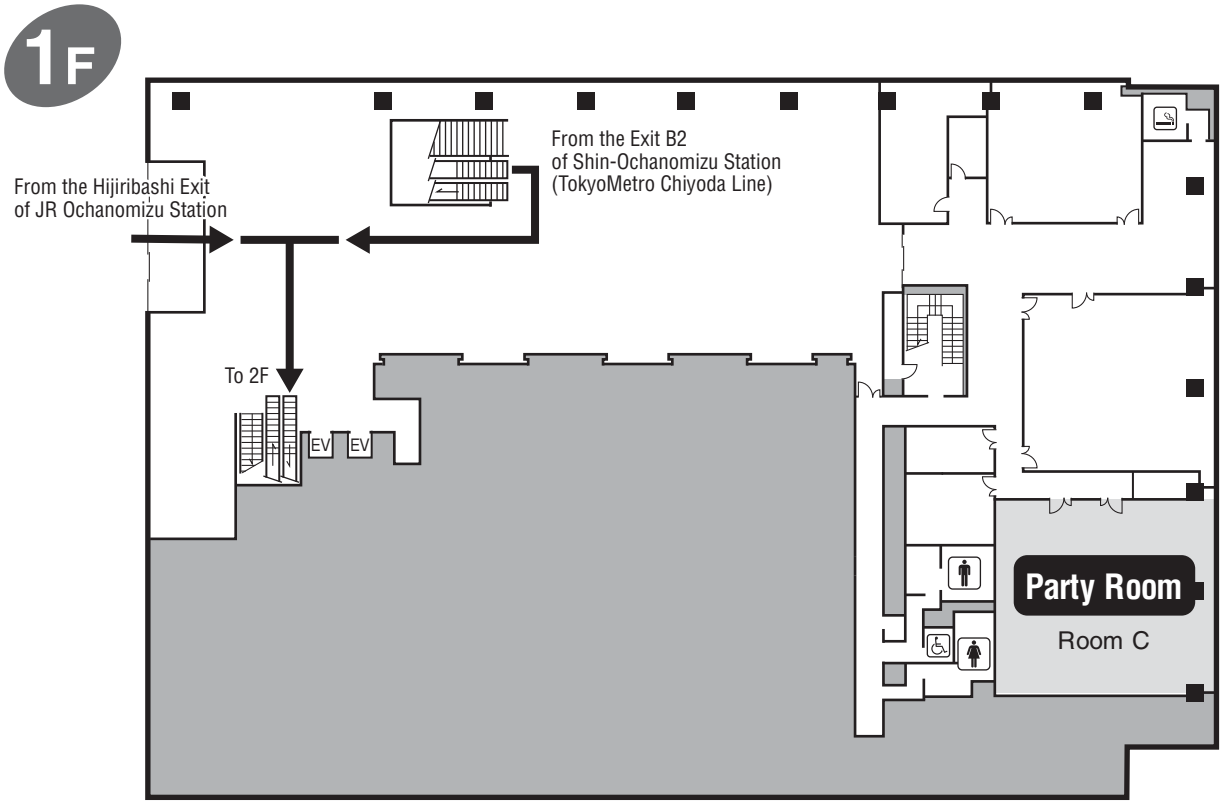


Venue Map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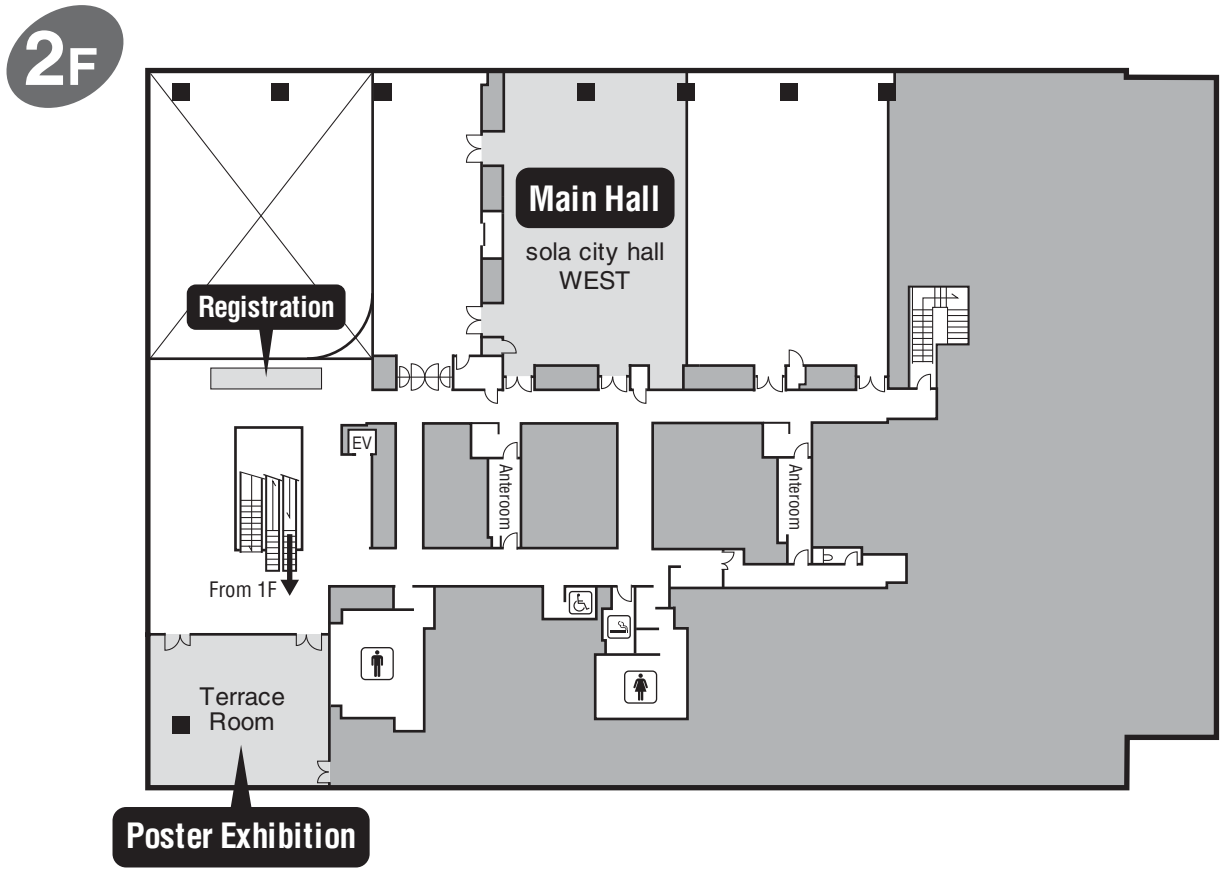
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Room
Poster Exhibition

Program

June 4（Saturday）

8:15- **Registration**

8:55-9:00 **Opening Remarks: Toshiaki Ohteki** (Chairman of MMCB 2016)

Symposium 1: Ontogeny and Identity of Mononuclear Phagocytes (9:00-11:30)

Chairpersons: **Florent Ginhoux** (Singapore Immunology Network, Singapore)
Toshiaki Ohteki (Tokyo Medical Dental University, Japan)

9:00-9:30 **S1-1** **Macrophage and Dendritic Cell Ontogeny**
Florent Ginhoux (Singapore Immunology Network, Singapore)

9:30-10:00 **S1-2** **Macrophages: Development and Tissue Specialization**
Steffen Jung (Weizmann Institute of Science, Israel)

10:00-10:30 **S1-3** **Ontogenetic Tracing of Dendritic Cells Reveals Unexpected Developmental Heterogeneity of Mononuclear Phagocytes**
Barbara Schraml (Klinikum der Universität München, Germany)

10:30-11:00 **S1-4** **Epigenetic regulation of monocyte and dendritic cell development by the transcription factor IRF8**
Tomohiko Tamura (Yokohama City University, Japan)

11:00-11:30 **S1-5** **Identification of Mononuclear Phagocyte Progenitors**
Toshiaki Ohteki (Tokyo Medical and Dental University, Japan)

Luncheon Seminar: Emerging Technology I (11:50-12:50)

(Supported by KYOWA KIRIN)

Chairperson: **Kiyoshi Takeda** (Osaka University, Japan)

11:50-12:50 **High dimensional, immunohistochemical imaging in clinical tissue biopsies using multiplexed ion beam imaging (MIBI)**
Michael Angelo (Stanford University, USA)

Symposium 2: Mononuclear Phagocytes in Infection and Inflammation (13:20-15:50)

Chairpersons: **Sho Yamasaki** (Kyushu University, Japan)
Osamu Takeuchi (Kyoto University, Japan)

13:20-13:50 **S2-1** **Heterogeneity of Intestinal Macrophages**
Milena Bogunovic (Penn State University College of Medicine, USA)

13:50-14:20 **S2-2** **The resolution of cerebral post-ischemic inflammation**
Takashi Shichita (Keio University, Japan)

14:20-14:50 **S2-3** **Regulation of Immune Responses through C-Type Lectin Receptors**
Sho Yamasaki (Kyushu University, Japan)

14:50-15:20 **S2-4** **Posttranscriptional control of inflammatory responses by Regnase-1 and Roquin**
Osamu Takeuchi (Kyoto University, Japan)

15:20-15:50 **S2-5** **Immuneregulation by CD169 Macrophages**
Masato Tanaka (Tokyo University of Pharmacy and Life Sciences, Japan)

16:00- **General Meeting (MMCB)**
Poster Presentation & Viewing

18:00-20:00 **Welcome Reception (Sola-City Conference Center, Room C)**

Symposium 1:
Ontogeny and Identity of Mononuclear Phagocytes

Chairpersons: **Florent Ginhoux** (Singapore Immunology Network, Singapore)
Toshiaki Ohteki (Tokyo Medical Dental University, Japan)

Speakers: **Florent Ginhoux** (Singapore Immunology Network, Singapore)
Steffen Jung (Weizmann Institute of Science, Israel)
Barbara Schraml (Klinikum der Universität München, Germany)
Tomohiko Tamura (Yokohama City University, Japan)
Toshiaki Ohteki (Tokyo Medical and Dental University, Japan)

S1-1 Macrophage and Dendritic Cell Ontogeny

Florent Ginhoux

Singapore Immunology Network (SIgN), Agency for Science, Technology and Research (A*STAR), Singapore Adjunct Visiting Associate Professor, Shanghai Immunology Institute, Jiao Tong University, China

Key Words: Macrophage, Monocyte, Dendritic Cell, Development, Differentiation

Dendritic cells (DCs), monocytes and macrophages play crucial and distinct roles in tissue homeostasis and immunity, but also contribute to a broad spectrum of pathologies and are thus attractive therapeutic targets. Potential intervention strategies aiming at manipulation of these cells will require in-depth insights of their origins and the mechanisms that govern their homeostasis.DCs and monocytes arise from common bone marrow (BM) precursor named macrophage-dendritic cell precursors (MDP), branching into exclusively DC- or monocyte-committed progenitors named common dendritic cell progenitors (CDPs) or common monocyte progenitor (cMoPs) respectively. CDPs give rise to plasmacytoid DC and migratory DC precursors termed pre-DCs. Pre-DCs seed tissues where they differentiate into the two major functionally specialized DC lineages, $CD8\alpha^+/CD103^+$ DC1 and $CD11b^+$ DC2.

Recent evidence from our laboratory and others have showed that monocytes do not substantially contribute to all tissue macrophage populations in steady state and inflammatory conditions. Rather certain tissue macrophages in mice are derived from embryonic precursors, are seeded before birth and maintain themselves in adults by self-renewal. In addition, we now provide evidence that commitment to DC1 and DC2 subsets is imprinted early in the BM. Combining single cell sequencing with conventional transcriptomic analysis, we identified for the first time DC subset-specific precursors in the BM as well as previously unknown molecular checkpoints for DC lineage commitment as early as the CDP stage. Using again single cell sequencing and CyTOF, we also identified homologous DC progenitors in humans and redefined the human DC lineage from the BM to the tissues.

These new insights into the origins of DCs, monocytes and macrophages should aid the rational design of therapies aimed at harnessing the functions of these cells in homeostasis and inflammation and will allow efficient targeting and manipulation during health and disease.

Symposium 2:
Mononuclear Phagocytes in Infection and Inflammation

Chairpersons: **Sho Yamasaki** (Kyushu University, Japan)
Osamu Takeuchi (Kyoto University, Japan)

Speakers: **Milena Bogunovic** (Penn State University College of Medicine, USA)
Takashi Shichita (Keio University, Japan)
Sho Yamasaki (Kyushu University, Japan)
Osamu Takeuchi (Kyoto University, Japan)
Masato Tanaka (Tokyo University of Pharmacy and Life Sciences, Japan)

S2-1 Heterogeneity of Intestinal Macrophages

Balazs Koscso, Kavitha Gowda, Milena Bogunovic

Penn State University College of Medicine, Milton S. Hershey Medical Center, Department of Microbiology and Immunology

Key Words: Intestine, Mucosa, Macrophages, Neurons, Infection

Macrophages are an essential component of the intestinal immune system. Their functions, however, exceed innate protection against pathogens that breach the intestinal mucosa. Intestinal macrophages are heterogeneous, as a distinct macrophage population resides in each intestinal layer, e.g., mucosa, submucosa and muscularis externa. Shaped by its unique microenvironment, each mononuclear phagocyte subset is developmentally and functionally unique and phenotypically distinct. To understand intra-intestinal subspecializations of macrophages we performed a transcriptome analysis of macrophages isolated from the mucosa and musculais externa. We identified unique gene signatures in mucosal versus muscularis macrophages, which reflected differences in their microenviroment and predicted their distinct functions. We have demonstrated that muscularis macrophages were anatomically associated with the enteric nervous system and we defined a central role of these innate immune cells in regulating GI physiology through crosstalk with enteric neurons. In contrast, mucosal macrophages provide a first line of defense against luminal pathogens. We have found that mucosal macrophages, not mucosal dendritic cells, are able to induce protective adaptive immune responses against enteroinvasive *Salmonella.*

Symposium 3:
Mononuclear Phagocytes in Immunometabolism

Chairpersons: **Makoto Arita** (RIKEN Center for Integrative Medical Sciences, Japan)
Toshiyuki Tanaka (Hyogo University of Health Sciences, Japan)

Speakers: **Vishwa Deep Dixit** (Yale School of Medicine, USA)
Minna Woo (University of Toronto , Canada)
Yoshinori Ogawa (Tokyo Medical and Dental University, Japan)
Michito Hamada (Tsukuba University, Japan)
Makoto Arita (RIKEN Center for Integrative Medical Sciences, Japan)

S3-1 The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease

Vishwa Deep Dixit

Comparative Medicine and Immunobiology, Yale School of Medicine,
New Haven, Connecticut, USA

Key Words: NLRP3, Inflammasome, β-hydroxybutyrate, Ketogenic diet, Inflammation

The ketone bodies b-hydroxybutyrate (BHB) and acetoacetate (AcAc) support mammalian survival during states of energy deficit by serving as alternative sources of ATP[1]. BHB levels are elevated by starvation, caloric restriction, high-intensity exercise, or the low-carbohydrate ketogenic diet[2]. Prolonged fasting reduces inflammation; however, the impact that ketones and other alternative metabolic fuels produced during energy deficits have on the innate immune response is unknown[2–6]. We report that BHB, but neither AcAc nor the structurally related short-chain fatty acids butyrate and acetate, suppresses activation of the NLRP3 inflammasome in response to urate crystals, ATP and lipotoxic fatty acids. BHB did not inhibit caspase-1 activation in response to pathogens that activate the NLR family, CARD domain containing 4 (NLRC4) or absent in melanoma 2 (AIM2) inflammasome and did not affect non-canonical caspase-11, inflammasome activation. Mechanistically, BHB inhibits the NLRP3 inflammasome by preventing K+ efflux and reducing ASC oligomerization and speck formation. The inhibitory effects of BHB on NLRP3 are not dependent on chirality or starvation-regulated mechanisms like AMP-activated protein kinase (AMPK), reactive oxygen species (ROS), autophagy or glycolytic inhibition. BHB blocks the NLRP3 inflammasome without undergoing oxidation in the TCA cycle, and independently of uncoupling protein-2 (UCP2), sirtuin-2 (SIRT2), the G protein–coupled receptor GPR109A or hydrocaboxylic acid receptor 2 (HCAR2). BHB reduces NLRP3 inflammasome–mediated interleukin (IL)-1b and IL-18 production in human monocytes. *In vivo*, BHB or a ketogenic diet attenuates caspase-1 activation and IL-1b secretion in mouse models of NLRP3-mediated diseases such as Muckle–Wells syndrome, familial cold autoinflammatory syndrome and urate crystal–induced peritonitis. Our findings suggest that the anti-inflammatory effects of caloric restriction or ketogenic diets may be linked to BHB-mediated inhibition of the NLRP3 inflammasome.

References

1. Newman, J.C. & Verdin, E. Ketone bodies as signaling metabolites. *Trends Endocrinol. Metab.* **25**, 42–52 (2014).
2. Cotter, D.G., Schugar, R.C. & Crawford, P.A. Ketone body metabolism and cardiovascular disease. *Am. J. Physiol. Heart Circ. Physiol*. **304**, H1060–H1076 (2013).
3. Shido, O., Nagasaka, T. & Watanabe, T. Blunted febrile response to intravenous endotoxin in starved rats. *J. Appl. Physiol.* **67**, 963–969 (1989).
4. Johnson, J.B. *et al.* Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radic. Biol. Med.* **42,** 665–674 (2007).
5. Mercken, E.M. *et al*. Calorie restriction in humans inhibits the PI3K/AKT pathway and induces a younger transcription profile. *Aging Cell* **12**, 645–651 (2013).
6. McGettrick, A.F. & O'Neill, L.A. How metabolism generates signals during innate immunity and inflammation. *J. Biol. Chem.* **288**, 22893–22898 (2013)

Symposium 4:
Mononuclear Phagocytes in Regeneration and Therapy

Chairpersons: **Ken J Ishii** (National Institute of Biomedical Innovation, Japan)
Kensuke Miyake (The University of Tokyo, Japan)

Speakers: **David J DiLillo** (The Rockefeller University, USA)
Takahiro Yamazaki (Gustave Roussy Cancer Campus, France)
Satoru Senju (Kumamoto University, Japan)
Kensuke Miyake (The University of Tokyo, Japan)
Ken J Ishii (National Institute of Biomedical Innovation, Japan)

S4-1 Differential Fc-receptor engagement drives an anti-tumor vaccinal effect

David J. DiLillo, Jeffrey V. Ravetch

The Rockefeller University, Laboratory of Molecular Genetics and Immunology, New York, NY, USA

Key Words: Fc-receptors, Antibodies, Dendritic Cells

Passively-administered anti-tumor mAbs rapidly kill tumor targets via FcγR-mediated cytotoxicity(ADCC), a short-term process. However, anti-tumor monoclonal antibody (mAb) treatment can also induce a vaccinal effect, in which mAb-mediated tumor death induces a long-term anti-tumor cellular immune response. To determine how such responses are generated, we utilized a murine model of an anti-tumor vaccinal effect against a model neoantigen. We demonstrate that FcγR expression by CD11c+ antigen-presenting cells is required to generate anti-tumor T cell responses upon ADCC-mediated tumor clearance. Using FcγR-humanized mice, we demonstrate that anti-tumor huIgG1 must engage hFcγRIIIA on macrophages to mediate ADCC, but also engage hFcγRIIA, the sole hFcγR expressed by human dendritic cells (DCs), to generate a potent vaccinal effect. Thus, while next-generation anti-tumor antibodies with enhanced binding to only hFcγRIIIA are now in clinical use, ideal anti-tumor antibodies must be optimized for both cytotoxic effects as well as hFcγRIIA engagement on DCs to stimulate long-term anti-tumor cellular immunity.

Luncheon Seminar:
Emerging Technology I

(Supported by KYOWA KIRIN)

Chairpersons: **Kiyoshi Takeda** (Osaka University, Japan)

Speakers: **Michael Angelo** (Stanford University, USA)

LS-1 High dimensional, immunohistochemical imaging in clinical tissue biopsies using multiplexed ion beam imaging (MIBI)

Michael Angelo
Pathology, Stanford University

Multiplexed ion beam imaging (MIBI) is a novel approach to immunohistochemistry (IHC) that uses secondary ion mass spectrometry (SIMS) and antibodies labeled with elemental mass tags to visualize dozens of proteins simultaneously in a single tissue section. MIBI is compatible with formalin-fixed, paraffin-embedded (FFPE) tissue specimens and can achieve single molecule sensitivity across a five log dynamic range. To permit broader use, we have constructed a novel imaging mass spectrometer capable of super resolution imaging and 100-fold faster sample throughput than previously reported. These tools are being used to comprehensively enumerate immune cell populations in normal and neoplastic solid tissues, to construct classifiers for predicting disease progression in pre-invasive cancer lesions, and to develop quantitative IHC assays to be used in a clinical setting.

Luncheon Seminar:
Emerging Technology II

(Supported by Fluidigm)

Chairpersons: **Atsushi Kumanogoh** (Osaka University, Japan)

Speakers: **Matthew Spitzer** (Stanford University, USA)

LS-2 Modeling Organism-Wide Immunity in Health and Cancer

Matthew H. Spitzer[1-5], Yaron Carmi[3], Nathan E. Reticker-Flynn[3], Pier Federico Gherardini[5], Garry P. Nolan[4, 5], and Edgar G. Engleman[3, 4]

1) Department of Microbiology and Immunology, University of California San Francisco, San Francisco, California, United States of America, 94143
2) Parker Institute for Cancer Immunotherapy, San Francisco, California, United States of America, 94143,
3) Department of Pathology,
4) Program in Immunology,
5) Baxter Laboratory, Department of Microbiology and Immunology, Stanford University School of Medicine, 269 Campus Drive, Stanford, California, United States of America, 94305

Key Words: Systems immunology, Immune responses, Tumor immunology, Cancer immunotherapy

Immune cells form a coordinated hierarchy to adapt to genetic and environmental contexts. We have recently developed graphical methods to build an extensible immune reference map from mass cytometry data[1]. The approach revealed unique organizational features of different tissues, influences of genetic and environmental variation on immune structure, and differences between murine and human blood organization. We have built on this foundation to reveal coordinated immune responses to during tumorigenesis, revealing a systematic rewiring of immune dynamics and function. Moreover, we demonstrate that this method is capable of modeling the effects of immunotherapeutic interventions on immune responses across the system, revealing the differences between tumor-eradicating[2] and unproductive immune responses against tumors.

References

1. Spitzer et al., *Science.* 2015 Jul 10; 349(6244): 1259425.
2. Carmi et al., *Nature*. 2015 May 7; 521(7550): 99-104.

Poster Presentation & Poster Viewing

P-01 An immunosugar-based heparanase inhibitor heparastatin (SF4) suppresses infiltration of neutrophils and monocytes into inflamed dorsal air pouches

Nobuaki Higashi[1)], Mayumi Sue[1)], Hiroaki Shida[1)], Yusuke Kogane[1)], Yoshio Nishimura[2)], Hayamitsu Adachi[2)], Elzbieta Kolaczkowska[3)], Magdalena Kepka[3)], Motowo Nakajima[4)], Tatsuro Irimura[1, 5)]

1) Graduate School of Pharmaceutical Sciences, The University of Tokyo
2) Institute of Microbial Chemistry, (BIKAKEN), Tokyo
3) Institute of Zoology, Jagiellonian University
4) SBI Pharmaceuticals Co., Ltd.
5) Juntendo University

Local infiltration of inflammatory cells is regulated by a number of biological steps during which the cells likely penetrate through subendothelial basement membranes that contain heparan sulfate proteoglycans. In the present study, we examined whether administration of heparastatin (SF4), an iminosugar-based inhibitor of heparanase, could suppress local inflammation and degradation of heparan sulfate proteoglycans in basement membranes. In a carrageenan- or formyl peptide-induced dorsal air pouch inflammation model, the number of infiltrated neutrophils and monocytes was significantly lower in mice after topical administration of heparastatin (SF4). The concentration of chemokines MIP-2 and KC in pouch exudates of drug-treated mice was similar to control. In a zymosan-induced peritonitis model, the number of infiltrated cells was not altered in drug-treated mice. To further test how heparastatin (SF4) influences transmigration of inflammatory neutrophils, its suppressive effect on migration and matrix degradation was examined in vitro. In the presence of heparastatin (SF4), the number of neutrophils that infiltrated across a Matrigel-coated polycarbonate membrane was significantly lower, while the number of neutrophils passing through an uncoated membrane was not altered. Lysate of bone marrow-derived neutrophils released sulfate-radiolabeled macromolecules from basement membrane-like extracellular matrix, which was suppressed by heparastatin (SF4). Heparan sulfate degradation activity was almost completely abolished after incubation of lysate with protein G-conjugated anti-heparanase monoclonal antibody, strongly suggesting that the activity was due to heparanase-mediated degradation. Taken together, in a dorsal air pouch inflammation model heparastatin (SF4) potentially suppresses extravasation of inflammatory cells by impairing the degradation of basement membrane heparan sulfate.

P-47 Access of protective antiviral antibody to neuronal tissues requires CD4 T-cell help

Norifumi Iijima[1, 2, 3], Akiko Iwasaki[3, 4]

1) Laboratory of Adjuvant Innovation, National Institute of Biomedical Innovation, Health and Nutrition
2) Immunology Frontier Research Center, Osaka University
3) Department of Immunobiology, Yale School of Medicine
4) Howard Hughes Medical Institute, Yale School of Medicine

Circulating antibodies can access most tissues to mediate surveillance and elimination of invading pathogens. Immunoprivileged tissues such as the brain and the peripheral nervous system are shielded from plasma proteins by the blood–brain barrier and blood–nerve barrier, respectively. Yet, circulating antibodies must somehow gain access to these tissues to mediate their antimicrobial functions. Here we examine the mechanism by which antibodies gain access to neuronal tissues to control infection. Using a mouse model of genital herpes infection, we demonstrate that both antibodies and CD4 T cells are required to protect the host after immunization at a distal site. We show that memory CD4 T cells migrate to the dorsal root ganglia and spinal cord in response to infection with herpes simplex virus type 2. Once inside these neuronal tissues, CD4 T cells secrete interferon-γ and mediate local increase in vascular permeability, enabling antibody access for viral control. A similar requirement for CD4 T cells for antibody access to the brain is observed after intranasal challenge with vesicular stomatitis virus. Our results reveal a previously unappreciated role of CD4 T cells in mobilizing antibodies to the peripheral sites of infection where they help to limit viral spread.

ICIS2017 in Kanazawa, Japan

Date: October 29 (Sun) - November 2 (Thu) , 2017

City: Kanazawa, Japan

Venue: Ishikawa Ongakudo (Main Hall)

Host Organization: International Cytokine and Interferon Society

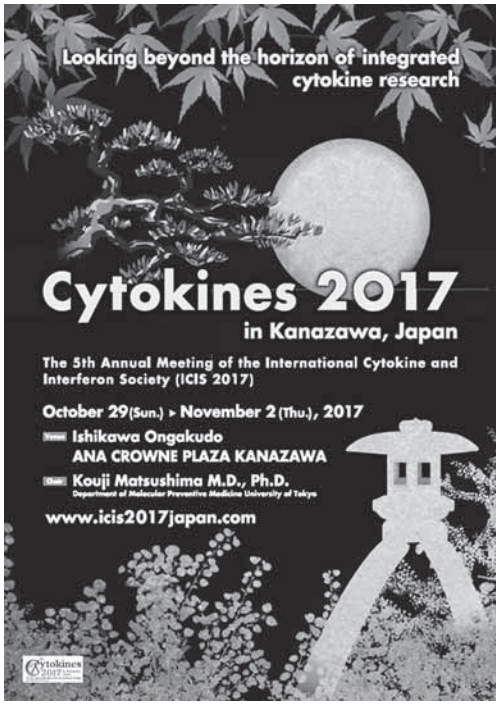
Co-host Organization: Japanese Society of Interferon & Cytokine ResearchJapanese Society for Molecular Cellular Biology of Macrophages

Local Organizing Committee Members:

President	Kouji Matsushima (University of Tokyo)
Honorary President	Tadamitsu Kishimoto (Osaka University)
Vice President	Yoichiro Iwakura (Tokyo University of Science) Takashi Fujita (Kyoto University) Shuichi Kaneko (Kanazawa University)
Program Chair	Akihiko Yoshimura (Keio University)
Secretary General	Naofumi Mukaida (Kanazawa University)

Main Theme: Looking beyond the horizon of integrated cytokine, interferon, and chemokine research

The Annual Meeting of the International Cytokine and Interferon Society 2017 will provide an outstanding forum for investigators in basic science and clinical research to present their most recent findings on the role of cytokines (including interferons, chemokines, and various pro-inflammatory/anti-inflammatory factors) in infection, cancer, allergy, autoimmunity, various other inflammatory/immune diseases, and novel therapeutic interventions.



Kanazawa is a beautiful city with a famous Samurai history and culture. A high-speed railway line from Tokyo to Kanazawa opened in March 2015, improving accessibility and reducing travel time from Tokyo to around 2.5 hours. Participants will enjoy the beauty of the Japanese Alps and the Sea of Japan coastline in their best season.

MMCB2016

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Macrophages 2016

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