



Hiroshi Watarai

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Education and Post

- 1987-1993 Graduate Student
Department of Biochemistry, Graduate School of
Agriculture and Life Sciences, The University of Tokyo
- 1993-2002 Research Scientist
Pharmaceutical Research Laboratories, Pharmaceutical
Division, Kirin Brewery Co. Ltd
- 2003-2006 Research Scientist
Riken Research Center for Allergy and Immunology
- 2006-2013 Senior Research Scientist
Riken Research Center for Allergy and Immunology
- 2014- present Division of Stem Cell Cellomics
Institute of Medical Science, University of Tokyo

Area of General Research

Molecular and cellular mechanisms in the inflammation

Current Research Program

1. Development of innovative basic technologies for systematically achieving serendipity.
2. Application of regenerative medicine focused on iPS technologies suitable for immunotherapy.
3. Eradication of the mechanisms in the induction of acute and chronic inflammation.
4. Immune regulation by the introduction of ligands for MHC class II-restricted T cells.

Recent Publications (Selected)

1. Ren Y, Sekine-Kondo E, Tateyama M, Kasattat T, Wongratanacheewin S, Watarai H. New genetically manipulated mice provide insights into the development and physiological functions of iNKT cells. *Front Immunol* in press (2018). doi: 10.3389/fimmu.2018.01294 (IF=6.429 in 2016/2017)
2. Mikami H, Harmon J, Kobayashi H, Hamad S, Wang Y, Iwata O, Suzuki K, Ito T, Aisaka Y, Kutsuna N, Nagasawa K, Watarai H, Ozeki Y, Goda K. Ultrafast confocal fluorescence microscopy beyond the fluorescence lifetime limit. *Optica* 5(2):117-126 (2018) . doi: 10.1364/OPTICA.5.000117. (IF=7.727 in 2016 /2017)
3. Ren Y, Sekine-Kondo E, Shibata R, Kato-Itoh M, Umino A, Yanagida A, Satoh M, Inoue K, Yamaguchi T, Mochida K, Nakae S, Van Kaer L, Iwabuchi K, Nakauchi H, Watarai

- H. A novel mouse model of iNKT cell-deficiency generated by CRISPR/Cas9 reveals a pathogenic role of iNKT cells in metabolic disease. *Sci Rep* 7(1):12765 (2017). doi: 10.1038/s41598-017-12475-4. (IF=5.228 in 2016 /2017)
4. Hayatsu N, Miyao T, Tachibana M, Murakami R, Kimura A, Kato T, Kawakami E, Endo TA, Setoguchi R, Watarai H, Nishikawa T, Yasuda T, Yoshida H, Hori S. Analyses of a mutant *Foxp3* allele reveal BATF as a critical transcription factor in the differentiation and accumulation of tissue regulatory T cells. *Immunity* 47(2):268 -283 (2017). doi: 10.1016/j.immuni.2017.07.008. (IF=22.845 in 2016 /2017)
5. Jinnohara T, Kanaya T, Hase K, Sakakibara S, Tachibana N, Hashimoto Y, Sato T, Watarai H, Kunisawa J, Shibata N, Williams IR, Kiyono H, Ohno H. IL -22BP dictates characteristics of Peyer's patch follicle-associated epithelium for antigen uptake. *J Exp Med* 214(6):1607 -1618 (2017). doi: 10.1084/jem.20160770. (IF=11.240 in 2016 /2017)
6. Taya Y, Ota Y, Wilkinson AC, Kanazawa A, Watarai H, Kasai M, Nakauchi H, Yamazaki S. Depleting dietary valine permits mouse hematopoietic stem cell transplantation. *Science* 354(6316):1152-1155 (2016). doi: 10.1126/science.aag3145 . (IF=37.205)
7. Ohashi W, Kimura S, Iwanaga T, Furusawa Y, Irié T, Izumi H, Watanabe T, Hijikata A, Hara T, Ohara O, Koseki H, Sato T, Robine S, Mori H, Hattori Y, Watarai H, Mishima K, Ohno H, Hase K, Fukada T. Zinc transporter SLC39A7/ZIP7 promotes intestinal epithelial self-renewal by resolving ER stress. *PLOS Genet* 12(10):e1006349 (2016). doi: 10.1371/journal.pgen.1006349 . (IF=6.100)
8. Wakisaka Y, Suzuki Y, Iwata O, Nakashima A, Ito T, Hirose M, Domon R, Sugawara M, Tsumura N, Watarai H, Shimobaba T, Suzuki K, Goda K, Ozeki Y. Probing the metabolic heterogeneity of live *Euglena gracilis* with label-free microscopy. *Nat Microbiol* 1(8):16124 (2016). doi: 10.1038/nmicrobiol.2016.124. (IF=not available)
9. Reynolds JM, Lee Y-H, Shi Y, Angkasekwinai P, Nallaparaju KC, Chang SH, Watarai H, Dong C. Interleukin-17B antagonizes interleukin-25-mediated mucosal inflammation. *Immunity* 42(4):692 -703 (2015). doi: 10.1016/j.immuni.2015.03.008. (IF=24.082)
10. Shimizu K, Sato Y, Shinga J, Watanabe T, Endo TA, Asakura M, Kawahara K, Kinjo Y, Kitamura H, Tsuji M, Watarai H, Ishii Y, Taniguchi M, Ohara O, Fujii SI. KLRG+ invariant natural killer T cells are long-lived effectors. *Proc Natl Acad Sci USA* 111(34):12474 -12479 (2014). doi: 10.1073/pnas.1406240111. (IF=9.674)
11. Ren Y, Dashtsoodol N, Watarai H, Koseki H, Quan C, Taniguchi M. Generation of induced pluripotent stem cell-derived mice by reprogramming of a mature natural killer T cell. *Int Immunol* 26(10):551-561 (2014). doi: 10.1093/intimm/dxu057. (IF=2.536)
12. Shimizuhira C, Otsuka A, Honda T, Kitoh A, Egawa G, Nakajima S, Nakashima C, Watarai H, Miyachi Y, Kabashima K. Natural killer T cells are essential for the development of contact hypersensitivity. *J Invest Dermatol* 134(11):2709-2718 (2014). doi: 10.1038/jid.2014.200. (IF=7.216)
13. Kitamura H, Kimura S, Shimamoto Y, Okabe J, Ito M, Miyamoto T, Naoe Y, Kikuguchi C, Meek B, Toda C, Okamoto S, Kanehira K, Hase K, Watarai H, Ishizuka M, El-Osta A,

Ohara O, Miyoshi I. Ubiquitin-specific protease 2-69 in macrophages potentially modulates metainflammation. *FASEB J* 27(12):4940 -4953 (2013). doi: 10.1096/fj.13-233528. (IF=5.480)

14. Mera T, Itoh T* , Kita S, Kodama S, Kojima D, Nishinakamura H, Okamoto K, Ohkura M, Nakai J, Iyoda T, Iwamoto T, Matsuda T, Baba A, Omori K, Ono J, Watarai H, Taniguchi M, Yasunami Y. Pretreatment of donor islets with the Na⁺/Ca²⁺-exchanger inhibitor improves the efficiency of islet transplantation. *Am J Transplant* 13(8):2154-2160 (2013). doi: 10.1111/ajt.12306. (IF=6.190)

15. Watarai H, Sekine -Kondo E, Motomura H, Yasuda T, Yoshida H, Kubo M, Koseki H, Taniguchi M. Development and function of invariant natural killer T cells producing TH2- and TH17-cytokines. *PLoS Biol* 10(2):e1001255 (2012). doi:10.1371/journal.pbio.1001255 . (IF=12.690)

16. Motomura Y, Kitamura H, Hijikata A, Matsunaga Y, Matsumoto K, Inoue H, Atarashi K, Hori S, Watarai H, Zhu J, Taniguchi M, Kubo M. The transcription factor E4BP4 regulates the production of IL -10 and IL-13 in CD4⁺ T cells. *Nat Immunol* 12(5):450 -459 (2011). doi: 10.1038/ni.2020. (IF=26.008)

17. Watarai H, Fujii SI, Yamada D, Rybouchkin A, Sakata S, Nagata Y, Iida-Kobayashi M, Sekine - Kondo E, Shimizu K, Shozaki Y, Sharif J, Matsuda M, Mochiduki S, Hasegawa T, Kitahara G, Endo T, Toyoda T, Ohara O, Harigaya KI, Koseki H, Taniguchi M. Murine induced pluripotent stem cells can be derived from and differentiate into natural killer T cells. *J Clin Invest* 120(7):2610 -2618 (2010). doi: 10.1172/JCI42027. (IF=14.152)

18. Angkasekwinai P, Chang SH, Thapa M, Watarai H, Dong C. Regulation of IL -9 expression by IL-25 signaling. *Nat Immunol* 11(3):250 -256 (2010). doi: 10.1038/ni.1846. (IF=25.688)

19. Matsuoka N, Itoh T, Watarai H, Sekine -Kondo E, Nagata N, Okamoto K, Mera T, Yamamoto H, Yamada S, Maruyama I, Taniguchi M, Yasunami Y ** . High -mobility group box 1 is involved in the initial events of early loss of transplanted islets in mice. *J Clin Invest* 120(3):735-743 (2010). doi: 10.1172/JCI41360. (IF=14.152)

20. Watarai H, Rybouchkin A, Hongo N, Nagata Y, Sakata S, Sekine E, Dashtsoodol N, Tashiro T, Fujii SI, Shimizu K, Mori K, Masuda K, Kawamoto H, Koseki H, Taniguchi M. Generation of functional NKT cells in vitro from embryonic stem cells bearing rearranged invariant Va14 -Ja18 TCR α gene. *Blood* 115(2):230-237 (2010). doi: 10.1182/blood-2009-04-217729. (IF=10.588)

21. Hase K, Kimura S, Takatsu H, Ohmae M, Kawano S, Kitamura H, Ito M, Watarai H, Hazelett CC, Yeaman C, Ohno H. M-Sec promotes membrane nanotube formation by interacting with Ral and the exocyst complex. *Nat Cell Biol* 11(12):1427 -1432 (2009). doi: 10.1038/ncb1990. (IF=19.527)

22. Terashima A, Watarai H, Inoue S, Sekine E, Nakagawa R, Hase K, Iwamura C, Nakajima H, Nakayama T, Taniguchi M. A novel subset of mouse NKT cells bearing the IL -17

receptor B responds to IL -25 and contributes to airway hyperreactivity. *J Exp Med* 205(12):2727-2733 (2008). doi: 10.1084/jem.20080698. (IF=15.219)

23. Watarai H, Sekine E, Inoue S, Nakagawa R, Kaisho T, Taniguchi M. PDC -TREM, a plasmacytoid dendritic cell -specific receptor, is responsible for augmented production of type I interferon. *Proc Natl Acad Sci USA* 105(8):2993 -2998 (2008). doi: 10.1073/pnas.0710351105 (IF=9.380)

24. Watarai H , Nakagawa R, Omori-Miyake M, Dashtsoodol N, Taniguchi M ** . Methods for detection, isolation and culture of mouse and human invariant NKT cells. *Nat Protoc* 3(1):70 -78 (2008). doi: 10.1038/nprot.2007.515. (IF=16.821)

25. Shinohara H, Maeda S, Watarai H, Kurosaki T. IkappaB kinase beta-induced m-phosphorylation of CARMA1 contributes to CARMA1 Bcl10 MALT1 complex formation in B cells. *J Exp Med* 204(13):3285-3293 (2007). doi: 10.1084/jem.20070379. (IF=15.612)

26. Harada M, Magara -Koyanagi K, Watarai H, Nagata Y, Ishii Y, Kojo S, Horiguchi S, Okamoto Y, Nakayama T, Suzuki N, Yeh WC, Akira S, Kitamura H, Ohara O, Seino K, Taniguchi M** . IL -21-induced B ϵ cell apoptosis mediated by natural killer T cells suppresses IgE responses. *J Exp Med* 203(13):2929- 2937 (2006). doi: 10.1084/jem.20062206. (IF=15.302)

27. Baba Y, Hayashi K, Fujii Y, Mizushima A, Watarai H, Wakamori M, Numaga T, Mori Y, Iino M, Hikida M, Ku rosaki T. Coupling of STIM1 to store-operated Ca²⁺entry through its constitutive and inducible movement in the endoplasmic reticulum. *Proc Natl Acad Sci USA* 103(45):16704 -16709 (2006). doi: 10.1073/pnas.0608358103. (IF=10.231)

28. Shinohara H, Yasuda T, Aiba Y, Sanjo H, Hamadate M, Watarai H, Sakurai H, Kurosaki T. PKC β regulates BCR-mediated IKK activation by facilitating the interaction between TAK1 and CARMA1. *J Exp Med* 202(10):1423-1431 (2005). doi: 10.1084/jem.20051591. (IF=13.965)

29. Watarai H, Hinohara A, Nagafune J, Nakayama T, Taniguchi M, Yamaguchi Y. Plasma membrane-focused proteomics: dramatic changes in surface expression during the maturation of human dendritic cells. *Proteomics* 5(15):4001- 4011 (2005). doi: 10.1002/pmic.200401258. (IF=6.088)

30. Kojo S, Seino K, Harada M, Watarai H, Wakao H, Uchida T, Nakayama T , Taniguchi M . Induction of regulatory properties in dendritic cells by V α 14 NKT cells. *J Immunol* 175(6):3648 -5365 (2005). doi: 10.4049/jimmunol.175.6.3648. (IF=6.387)

31. Kimura MY, Hosokawa H, Yamashita M, Hasegawa A, Iwamura C, Watarai H, Taniguchi M, Takagi T, Ishii S, Nakayama T ** . Regulation of T helper type 2 cell differentiation by murine Schnurri -2. *J Exp Med* 201(3):397-408 (2005). doi:10.1084/jem.20040733. (IF=13.965)