

CURRICULUM VITAE

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NAME: Kouji Matsushima

POSITION: Professor

AFFILIATION AND ADDRESS:

Division of Molecular Regulation of Inflammatory and Immune Diseases,
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EDUCATION:

March 1978 - M.D., Kanazawa University, School of Medicine,
Kanazawa, Japan.

March 1982 - Ph.D., Kanazawa University, Graduate School of
Medicine, Kanazawa, Japan.

CAREER HISTORY:

1982-1983 Visiting Fellow, National Institute of Dental Research, Bethesda, MD, USA.

1983-1990 Lab. of Molecular Immunoregulation, Biological Response Modifiers Program,
National Cancer Institute, Frederick, MD, USA (1983-1985 Visiting Fellow;
1985-1987 Visiting Associate; 1987-1990 Visiting Scientist (offered a tenure
position in 1989)).

1990-1997 Professor of the Dept. of Pharmacology, Cancer Research Institute, Kanazawa
University, Kanazawa, Japan.

1996-2018 Professor of the Dept. of Molecular Preventive Medicine, Graduate School of
Medicine, The University of Tokyo, Tokyo, Japan.

2018-present Professor of the Division of Molecular Regulation of Inflammatory and Immune
Diseases, Research Institute for Biomedical Sciences, Tokyo University of Science,
Chiba, Japan.

MAJOR SCIENTIFIC CONTRIBUTION:

- 1) Purification of human interleukin 1 alpha and beta, and identifying N-terminal of mature form of IL 1 beta
- 2) Discovery of prototypes of chemokines, Interleukin 8 (CXCL8) and MCAF(MCP-1, CCL2)
- 3) Clinical development of humanized anti-CCR4 antibody against ATLL

OTHER WORKS:

- 1) First description of the induction of Mn-superoxide dismutase in response to external stimuli

in eukaryotes

- 2) Identification of interleukin 1 as a monocyte/macrophage activating factor to be cytotoxic to tumors
- 3) Interleukin 1 has TNF-like activity, direct tumor-cytotoxic activity
- 4) Discovery of ADAM-TS-1
- 5) Discovery of CCR2-associated molecule, FROUNT

SUMMARY OF PRESENT WORK:

Main goal of our research is providing novel ways and targets for preventing and treating intractable inflammatory and immune diseases through revealing their molecular and cellular mechanisms. Current interest of my laboratory is chronic inflammation-associated organ fibrosis and tumorigenesis and the development of innovative methods to cure cancer through novel combination immunotherapy.

MAIN ACADEMIC SOCIETIES:

- The American Association of Immunologists
- International Cytokine Society (Past Senior Council Member)
- International Association of Inflammation Societies (President 2011-2013)
- The Japanese Society for Cancer Research
- The Japanese Society for Immunology
(Senior Council Member, 1999-2002, 2004-2008 and 2010-2014)
- The Japanese Society for Inflammation and Regeneration
(Senior Council Member, 2001-present. President, 2010-2012)
- The Japanese Society of Molecular Cell Biology of Macrophages
(President, 1995- 2016)
- The Japanese Society of Interferon and Cytokine Research
(President, 2006- 2008)

AWARDS:

- 1991-Public Health Special Recognition Award from DHHS, USA. Interleukin 8 and monocyte chemotactic and activating factor
- 1998-Takaoka Citizen Culture Award
- 2012-Japanese Cancer Association-CHAAO Award
- 2015-The Pharmaceutical Society of Japan, Drug Development Science Award
- 2016-Japanese Minister of Culture and Science Award
- 2016-Japanese Society of Immunology Human Immunology Research Award
- 2019-International Cytokine and Interferon Society The Lifetime Honorary Membership Award
- 2020-Toray Science and Technology Prize, Contribution to the treatment of intractable immune diseases through the research on inflammation regulators.
- 2021- Takeda Prize for Medical Science, Revealing the mechanisms of leukocyte infiltration through the discovery of chemokines and contribution to the drug development.

ORIGINAL ARTICLES AND REVIEWS:

1. Hirose Y, Konda S, Sugai S, Takiguchi T, Shimizu S, Matsushima K, Annen Y. A case of eosinophilic leukemia associated with Loffler's endocarditis. Clinical course and autopsy findings. *Nippon Ketsueki Gakkai Zasshi*. 44:902-909, 1981.
2. Matsushima K, Cheng M, Migita S. Purification and physicochemical characterization of human alpha 2-HS-glycoprotein. *Biochim Biophys Acta*. 701:200-205, 1982.
3. Akiyama Y, Stevenson GW, Schlick E, Matsushima K, Miller PJ, Stevenson HC. Differential ability of human blood monocyte subsets to release various cytokines. *J Leukoc Biol*. 37:519-530, 1985.
4. Auron PE, Rosenwasser LJ, Matsushima K, Copeland T, Dinarello CA, Oppenheim JJ, Webb AC. Human and murine interleukin 1 possess sequence and structural similarities. *J Mol Cell Immunol*. 2:169-177, 1985.
5. Matsushima K, Bano M, Kidwell WR, Oppenheim JJ. Interleukin 1 increases collagen type IV production by murine mammary epithelial cells. *J Immunol*. 134:904-909, 1985.
6. Matsushima K, Durum SK, Kimball ES, Oppenheim JJ. Purification of human interleukin 1 from human monocyte culture supernatants and identity of thymocyte comitogenic factor, fibroblast-proliferation factor, acute-phase protein-inducing factor, and endogenous pyrogen. *Cell Immunol*. 92:290-301, 1985.
7. Matsushima K, Kuang YD, Tosato G, Hopkins SJ, Oppenheim JJ. B-cell-derived interleukin 1 (IL-1)-like factor. I. Relationship of production of IL-1-like factor to accessory cell function of Epstein-Barr virus-transformed human B-lymphoblast lines. *Cell Immunol*. 94:406-417, 1985.
8. Matsushima K, Oppenheim JJ. Calcium ionophore (A23187) increases interleukin 1 (IL-1) production by human peripheral blood monocytes and interacts synergistically with IL-1 to augment concanavalin A stimulated thymocyte proliferation. *Cell Immunol*. 90:226-233, 1985.
9. Matsushima K, Procopio A, Abe H, Scala G, Ortaldo JR, Oppenheim JJ. Production of interleukin 1 activity by normal human peripheral blood B lymphocytes. *J Immunol*. 135:1132-1136, 1985.
10. Matsushima K, Tosato G, Benjamin D, Oppenheim JJ. B-cell-derived interleukin-1 (IL-1)-like factor. II. Sources, effects, and biochemical properties. *Cell Immunol*. 94:418-426, 1985.
11. Onozaki K, Matsushima K, Aggarwal BB, Oppenheim JJ. Human interleukin 1 is a cytotoxic factor for several tumor cell lines. *J Immunol*. 135:3962-3968, 1985.
12. Onozaki K, Matsushima K, Kleinerman ES, Saito T, Oppenheim JJ. Role of interleukin 1 in promoting human monocyte-mediated tumor cytotoxicity. *J Immunol*. 135:314-320, 1985.
13. Abe H, Rossio JL, Ruscetti FW, Matsushima K, Oppenheim JJ. Establishment of a human B cell line that proliferates in response to B cell growth factor. *J Immunol Methods*. 90:111-123, 1986.
14. Endo Y, Matsushima K, Oppenheim JJ. Mechanism of in vitro antitumor effects of interleukin 1 (IL 1). *Immunobiology*. 172:316-322, 1986.

15. Matsushima K, Akahoshi T, Yamada M, Furutani Y, Oppenheim JJ. Properties of a specific interleukin 1 (IL 1) receptor on human Epstein Barr virus-transformed B lymphocytes: identity of the receptor for IL 1-alpha and IL 1-beta. *J Immunol.* 136:4496-4502, 1986.
16. Matsushima K, Copeland TD, Onozaki K, Oppenheim JJ. Purification and biochemical characteristics of two distinct human interleukins 1 from the myelomonocytic THP-1 cell line. *Biochemistry.* 25:3424-3429, 1986.
17. Matsushima K, Taguchi M, Kovacs EJ, Young HA, Oppenheim JJ. Intracellular localization of human monocyte associated interleukin 1 (IL 1) activity and release of biologically active IL 1 from monocytes by trypsin and plasmin. *J Immunol.* 136:2883-2891, 1986.
18. Matsushima K, Yodoi J, Tagaya Y, Oppenheim JJ. Down-regulation of interleukin 1 (IL 1) receptor expression by IL 1 and fate of internalized 125I-labeled IL 1 beta in a human large granular lymphocyte cell line. *J Immunol.* 137:3183-3188, 1986.
19. Oppenheim JJ, Kovacs EJ, Matsushima K, Durum SK. There is more than one interleukin 1. *Immunol. Today* 2: 45-56, 1986.
20. Kasahara T, Mukaida N, Shinomiya H, Imai M, Matsushima K, Wakasugi H, Nakano K. Preparation and characterization of polyclonal and monoclonal antibodies against human interleukin 1 alpha (IL 1 alpha). *J Immunol.* 138:1804-1812, 1987.
21. Kawano M, Matsushima K, Oppenheim JJ. Identification of a major 50-kDa molecular weight human B-cell growth factor with Tac antigen-inducing activity on B cells. *Cell Immunol.* 108:132-149, 1987.
22. Matsushima K, Akahoshi T, Oppenheim JJ. Regulation of interleukin-1 (IL-1) receptor expression and protein phosphorylation induced by IL-1 stimulation. *Ann Inst Pasteur Immunol.* 138:478-481, 1987.
23. Matsushima K, Kobayashi Y, Copeland TD, Akahoshi T, Oppenheim JJ. Phosphorylation of a cytosolic 65-kDa protein induced by interleukin 1 in glucocorticoid pretreated normal human peripheral blood mononuclear leukocytes. *J Immunol.* 139:3367-3374, 1987.
24. Onozaki K, Tamatani T, Hashimoto T, Matsushima K. Growth inhibition and augmentation of mouse myeloid leukemic cell line differentiation by interleukin 1. *Cancer Res.* 47:2397-2402, 1987.
25. Oppenheim JJ, Matsushima K, Yoshimura T, Leonard EJ. The activities of cytokines are pleiotropic and interdependent. *Immunol Lett.* 16:179-183, 1987.
26. Yodoi J, Okada M, Tagaya Y, Taniguchi Y, Teshigawara K, Kasahara T, Dinarello CA, Matsushima K, Honko T, Uchiyama T, et al. IL-2 receptor gene activation by ATL-derived factor (ADF). *Adv Exp Med Biol.* 213:139-148, 1987.
27. Yoshimura T, Matsushima K, Oppenheim JJ, Leonard EJ. Neutrophil chemotactic factor produced by lipopolysaccharide (LPS)-stimulated human blood mononuclear leukocytes: partial characterization and separation from interleukin 1 (IL 1). *J Immunol.* 139:788-793, 1987.
28. Yoshimura T, Matsushima K, Tanaka S, Robinson EA, Appella E, Oppenheim JJ, Leonard EJ. Purification of a human monocyte-derived neutrophil chemotactic factor that has peptide sequence similarity to other host defense cytokines. *Proc Natl Acad Sci U S A.* 84:9233-9237,

- 1987.
29. Akahoshi T, Oppenheim JJ, Matsushima K. Interleukin 1 stimulates its own receptor expression on human fibroblasts through the endogenous production of prostaglandin(s). *J Clin Invest.* 82:1219-1224, 1988.
 30. Akahoshi T, Oppenheim JJ, Matsushima K. Induction of high-affinity interleukin 1 receptor on human peripheral blood lymphocytes by glucocorticoid hormones. *J Exp Med.* 167:924-936, 1988.
 31. Endo Y, Matsushima K, Onozaki K, Oppenheim JJ. Role of ornithine decarboxylase in the regulation of cell growth by IL-1 and tumor necrosis factor. *J Immunol.* 141:2342-2348, 1988.
 32. Kawano M, Matsushima K, Masuda A, Oppenheim JJ. A major 50-kDa human B-cell growth factor-II induces both Tac antigen expression and proliferation by several types of lymphocytes. *Cell Immunol.* 111:273-286, 1988.
 33. Kobayashi Y, Appella E, Yamada M, Copeland TD, Oppenheim JJ, Matsushima K. Phosphorylation of intracellular precursors of human IL-1. *J Immunol.* 140:2279-2287, 1988.
 34. Lavu S, Clark J, Swarup R, Matsushima K, Paturu K, Moss J, Kung HF. Molecular cloning and DNA sequence analysis of the human guanine nucleotide-binding protein Go alpha. *Biochem Biophys Res Commun.* 150:811-815, 1988.
 35. Lew W, Oppenheim JJ, Matsushima K. Analysis of the suppression of IL-1 alpha and IL-1 beta production in human peripheral blood mononuclear adherent cells by a glucocorticoid hormone. *J Immunol.* 140:1895-1902, 1988.
 36. Masuda A, Longo DL, Kobayashi Y, Appella E, Oppenheim JJ, Matsushima K. Induction of mitochondrial manganese superoxide dismutase by interleukin 1. *Faseb J.* 2:3087-3091, 1988.
 37. Matsushima K, Morishita K, Yoshimura T, Lavu S, Kobayashi Y, Lew W, Appella E, Kung HF, Leonard EJ, Oppenheim JJ. Molecular cloning of a human monocyte-derived neutrophil chemotactic factor (MDNCF) and the induction of MDNCF mRNA by interleukin 1 and tumor necrosis factor. *J Exp Med.* 167:1883-1893, 1988.
 38. Matsushima K, Shiroy M, Kung HF, Copeland TD. Purification and characterization of a cytosolic 65-kilodalton phosphoprotein in human leukocytes whose phosphorylation is augmented by stimulation with interleukin 1. *Biochemistry.* 27:3765-3770, 1988.
 39. Merrill JE, Matsushima K. Production of and response to interleukin 1 by cloned human oligodendrogloma cell lines. *J Biol Regul Homeost Agents.* 2:77-86, 1988.
 40. Modi WS, Masuda A, Yamada M, Oppenheim JJ, Matsushima K, O'Brien SJ. Chromosomal localization of the human interleukin 1 alpha (IL-1 alpha) gene. *Genomics.* 2:310-314, 1988.
 41. Oppenheim JJ, Lew W, Akahoshi T, Matsushima K, Neta R. Aspects of cytokine induced modulation of immunity and inflammation with emphasis on interleukin 1. *Arzneimittelforschung.* 38:461-465, 1988.
 42. Tagaya Y, Okada M, Sugie K, Kasahara T, Kondo N, Hamuro J, Matsushima K, Dinarello CA, Yodoi J. IL-2 receptor(p55)/Tac-inducing factor. Purification and characterization of adult T cell leukemia-derived factor. *J Immunol.* 140:2614-2620, 1988.

43. Tanaka S, Robinson EA, Yoshimura T, Matsushima K, Leonard EJ, Appella E. Synthesis and biological characterization of monocyte-derived neutrophil chemotactic factor. *FEBS Lett.* 236:467-470, 1988.
44. Clore GM, Appella E, Yamada M, Matsushima K, Gronenborn AM. Determination of the secondary structure of interleukin-8 by nuclear magnetic resonance spectroscopy. *J Biol Chem.* 264:18907-18911, 1989.
45. Furutani Y, Nomura H, Notake M, Oyamada Y, Fukui T, Yamada M, Larsen CG, Oppenheim JJ, Matsushima K. Cloning and sequencing of the cDNA for human monocyte chemotactic and activating factor (MCAF). *Biochem Biophys Res Commun.* 159:249-255, 1989.
46. Larsen CG, Anderson AO, Appella E, Oppenheim JJ, Matsushima K. The neutrophil-activating protein (NAP-1) is also chemotactic for T lymphocytes. *Science.* 243:1464-1466, 1989.
47. Larsen CG, Anderson AO, Oppenheim JJ, Matsushima K. Production of interleukin-8 by human dermal fibroblasts and keratinocytes in response to interleukin-1 or tumour necrosis factor. *Immunology.* 68:31-36, 1989.
48. Larsen CG, Zachariae CO, Oppenheim JJ, Matsushima K. Production of monocyte chemotactic and activating factor (MCAF) by human dermal fibroblasts in response to interleukin 1 or tumor necrosis factor. *Biochem Biophys Res Commun.* 160:1403-1408, 1989.
49. Matsushima K, Larsen CG, DuBois GC, Oppenheim JJ. Purification and characterization of a novel monocyte chemotactic and activating factor produced by a human myelomonocytic cell line. *J Exp Med.* 169:1485-1490, 1989.
50. Matsushima K, Oppenheim JJ. Interleukin 8 and MCAF: novel inflammatory cytokines inducible by IL 1 and TNF. *Cytokine.* 1:2-13, 1989.
51. Morinaga Y, Suzuki H, Takatsuki F, Akiyama Y, Taniyama T, Matsushima K, Onozaki K. Contribution of IL-6 to the antiproliferative effect of IL-1 and tumor necrosis factor on tumor cell lines. *J Immunol.* 143:3538-3542, 1989.
52. Mukaida N, Shiroo M, Matsushima K. Genomic structure of the human monocyte-derived neutrophil chemotactic factor IL-8. *J Immunol.* 143:1366-1371, 1989.
53. Nakao S, Matsushima K, Young N. Decreased interleukin 1 production in aplastic anaemia. *Br J Haematol.* 71:431-436, 1989.
54. Oppenheim JJ, Matsushima K, Yoshimura T, Leonard EJ, Neta R. Relationship between interleukin 1 (IL1), tumor necrosis factor (TNF) and a neutrophil attracting peptide (NAP-1). *Agents Actions.* 26:134-140, 1989.
55. Samanta AK, Oppenheim JJ, Matsushima K. Identification and characterization of specific receptors for monocyte-derived neutrophil chemotactic factor (MDNCF) on human neutrophils. *J Exp Med.* 169:1185-1189, 1989.
56. Yoshimura T, Robinson EA, Appella E, Matsushima K, Showalter SD, Skeel A, Leonard EJ. Three forms of monocyte-derived neutrophil chemotactic factor (MDNCF) distinguished by different lengths of the amino-terminal sequence. *Mol Immunol.* 26:87-93, 1989.
57. Appella E, Matsushima K, Oppenheim JJ, Yoshimura T, Leonard EJ, Clore GM, Gronenborn

- AM. Determination of the primary and secondary structure of NAP-1/IL-8 and a monocyte chemoattractant protein, MCP-1/MCAF. *Prog Clin Biol Res.* 349:405-417, 1990.
58. Baldwin ET, Franklin KA, Appella E, Yamada M, Matsushima K, Wlodawer A, Weber IT. Crystallization of human interleukin-8. A protein chemotactic for neutrophils and T-lymphocytes. *J Biol Chem.* 265:6851-6853, 1990.
 59. Balentien E, Han JH, Thomas HG, Wen DZ, Samantha AK, Zachariae CO, Griffin PR, Brachmann R, Wong WL, Matsushima K, Richmond A. Recombinant expression, biochemical characterization, and biological activities of the human MGSA/gro protein. *Biochemistry.* 29:10225-10233, 1990.
 60. Brennan FM, Zachariae CO, Chantry D, Larsen CG, Turner M, Maini RN, Matsushima K, Feldmann M. Detection of interleukin 8 biological activity in synovial fluids from patients with rheumatoid arthritis and production of interleukin 8 mRNA by isolated synovial cells. *Eur J Immunol.* 20:2141-2144, 1990.
 61. Clore GM, Appella E, Yamada M, Matsushima K, Gronenborn AM. Three-dimensional structure of interleukin 8 in solution. *Biochemistry.* 29:1689-1696, 1990.
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 64. Kobayashi Y, Oppenheim JJ, Matsushima K. Calcium-dependent binding of phosphorylated human pre interleukin 1 alpha to phospholipids. *J Biochem (Tokyo).* 107:666-670, 1990.
 65. Kobayashi Y, Yamamoto K, Saïdo T, Kawasaki H, Oppenheim JJ, Matsushima K. Identification of calcium-activated neutral protease as a processing enzyme of human interleukin 1 alpha. *Proc Natl Acad Sci U S A.* 87:5548-5552, 1990.
 66. Larsen C, Zachariae C, Mukaida N, Anderson A, Yamada M, Oppenheim J, Matsushima K. Proinflammatory cytokines interleukin 1 and tumor necrosis factor induce cytokines that are chemotactic for neutrophils, T cells and monocytes. *Prog Clin Biol Res.* 349:419-431, 1990.
 67. Modi WS, Dean M, Seuanez HN, Mukaida N, Matsushima K, O'Brien SJ. Monocyte-derived neutrophil chemotactic factor (MDNCF/IL-8) resides in a gene cluster along with several other members of the platelet factor 4 gene superfamily. *Hum Genet.* 84:185-187, 1990.
 68. Mukaida N, Mahe Y, Matsushima K. Cooperative interaction of nuclear factor-kappa B- and cis-regulatory enhancer binding protein-like factor binding elements in activating the interleukin-8 gene by pro-inflammatory cytokines. *J Biol Chem.* 265:21128-21133, 1990.
 69. Samanta AK, Oppenheim JJ, Matsushima K. Interleukin 8 (monocyte-derived neutrophil chemotactic factor) dynamically regulates its own receptor expression on human neutrophils. *J Biol Chem.* 265:183-189, 1990.
 70. Shiroo M, Matsushima K. Enhanced phosphorylation of 65 and 74 kDa proteins by tumor necrosis factor and interleukin-1 in human peripheral blood mononuclear cells. *Cytokine.* 2:13-20, 1990.

71. Sica A, Matsushima K, Van Damme J, Wang JM, Polentarutti N, Dejana E, Colotta F, Mantovani A. IL-1 transcriptionally activates the neutrophil chemotactic factor/IL-8 gene in endothelial cells. *Immunology*. 69:548-553, 1990.
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- human fibrosarcoma cell line. *Immunology*. 75:674-679, 1992.
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