

Research Center for Medical Sciences Core Research Facilities for Basic Science (Division of Molecular Genetics)

Mayumi Tamari, *Professor*
Yuji Ohno, *Assistant Professor*

Yumi Kanegae, *Associate Professor*
Tomomitsu Hirota, *Assistant Professor*

General Summary

Recent advances in technologies and study designs have unveiled the genetic components of human diseases. The aim of our project is to explore genetic factors of allergic and immunological diseases. Interdisciplinary research to elucidate the relationships between genetic variants and phenotypes is necessary to identify the molecular targets and improve our understanding of diseases.

Gene therapy has become an attractive procedure to cure diseases. We contribute to gene therapy through the development of regulation of gene-expression and genome editing.

We maintain the following experimental devices, which are commonly utilized: next-generation sequencing systems, 3130XL sequencer, MoFlo XDP cell sorter, flow cytometer, X-ray irradiation research system and qPCR. We also support experiments using these devices.

Research Activities

Genetics of inflammatory diseases

Psoriasis is an inflammatory skin disease histologically characterized by epidermal hyperplasia, inflammatory cell infiltration and vascular changes. A dysregulated cutaneous immune response occurs in genetically susceptible individuals. We have collaborated with Osaka University and Nippon Medical University for researching inflammatory skin diseases since 2017. We have recruited patients with psoriasis and conducted an association study of psoriasis with GWAS-discovered loci for psoriasis. We are going to perform genome-wide association study, next-generation sequencing analysis, transcriptome and metabolome analysis of psoriasis.

An effective strategy for the research of allergic and immunological diseases

Starting in August 2017, Prof. Tamari has served as the principal investigator of a group established to make research plans for the next ten years of allergy and clinical immunology research. This work is supported by Health Science Research Grants from the Ministry of Health, Welfare and Labor of Japan and we are going to compile a report on an effective strategy for the research of allergic and immunological diseases.

Development of the adenovirus vector systems

Because the adenovirus vector (AdV) is an attractive tool for gene expression and for the regulation of gene expression, it is applied to many areas of research. It is well known

that the AdV is useful tool to transduce the purpose gene in hepatocytes. We develop a protocol for cure of hepatitis B virus (HBV) using AdV. In culture cells, the efficiency of HBV genome replication is poor. We established the efficient detection system of HBV genome replication applying AdVs (HBV103-AdV system). We performed high-throughput screening of anti-HBV drugs using this system. As a result, we identified several promising compounds and analyzed the mechanism. Furthermore, we succeeded in efficient cleavage of HBV genome using CRISPR/Cas9 and now we develop a hepatocyte specific genome editing system. And also we have constructed the AdVs for repairing Gusb gene of Sly's disease by genome editing.

Publications

- Kanazawa J¹, Masuko H¹, Yatagai Y¹, Sakamoto T¹, Yamada H¹, Kaneko Y¹, Kitazawa H¹, Iijima H², Naito T², Saito T², Noguchi E², Konno S⁴, Nishimura M¹, Hirota T, Tamari M, Hizawa N¹** (¹Tsukuba Univ, ²Tsukuba Medical Center, ³Ibaraki National Hosp, ⁴Hokkaido Univ). Genetic association of the functional CDHR3 genotype with early-onset adult asthma in Japanese populations. *Allergol Int.* 2017; **66**: 563-7.
- Sunadome H^{1,2}, Matsumoto H^{1,2}, Petrova G¹, Kanemitsu Y¹, Tohda Y^{2,3}, Horiguchi T^{2,4}, Kita H^{2,5}, Kuwabara K^{2,4}, Tomii K^{2,6}, Otsuka K^{2,6}, Fujimura M^{2,7}, Ohkura N^{2,7}, Tomita K^{2,5}, Yokoyama A^{2,8}, Ohnishi H^{2,8}, Nakano Y^{2,9}, Oguma T^{2,9}, Hozawa S^{2,10}, Nagasaki T¹, Ito I¹, Oguma T¹, Inoue H¹, Tajiri T¹, Iwata T¹, Izuhara Y¹, Ono J¹¹, Ohta S¹², Hirota T, Tamari M, Yokoyama T¹³, Niimi A^{1,2,14}, Izuhara K¹², Mishima M^{1,2}** (¹Kyoto Univ, ²KiHAC, ³Kinki Univ, ⁴Fujita Health University Second Educational Hosp, ⁵Takatsuki Red Cross Hosp, ⁶Kobe City Medical Center General Hosp, ⁷Kanazawa Univ, ⁸Kochi Univ, ⁹Shiga Univ, ¹⁰Hiroshima Allergy and Respiratory Clinic, ¹¹Shino-Test Corporation, ¹²Saga Med Sch, ¹³National Institute of Public Health, ¹⁴Nagoya City University School of Medical Sciences). IL4R α and ADAM33 as genetic markers in asthma exacerbations and type-2 inflammatory endotype. *Clin Exp Allergy.* 2017; **47**: 998-1006.
- Hirota T, Nakayama T, Sato S¹, Yanagida N¹, Matsui T², Sugiura S², Takaoka Y², Hizawa N⁴, Fujieda S⁵, Miyatake A⁶, Sasaki T⁷, Amagai M¹, Doi S³, Ito K², Ebisawa M¹, Tamari M** (¹Sagamihara National Hosp, ²Aichi Children's Health and Medical Center, ³Osaka Prefectural Medical Center for Respiratory and Allergic Diseases, ⁴Tsukuba Univ, ⁵Fukui Univ, ⁶Miyatake Asthma Clinic, ⁷Keio Univ). Association study of childhood food allergy with GWAS-discovered loci of atopic dermatitis and eosinophilic esophagitis. *J Allergy Clin Immunol.* 2017; **140**: 1713-6.
- Inoue H^{1,2}, Ito I¹, Niimi A³, Matsumoto H¹, Oguma T¹, Tajiri T¹, Iwata T¹, Nagasaki T¹, Kanemitsu Y¹, Morishima T⁴, Hirota T, Tamari M, Wenzel SE², Mishima M¹** (¹Kyoto Univ, ²Pittsburgh Univ, ³Nagoya City Univ, ⁴Osaka Medical Center for Cancer and Cardiovascular Diseases). Association of interleukin 1 receptor-like 1 gene polymorphisms with eosinophilic phenotype in Japanese adults with asthma. *Respiratory Investigation.* 2017; **55**: 338-47.
- Hirata J^{1,2}, Hirota T, Ozeki T³, Kanai M^{1,2}, Sudo T⁴, Tanaka T⁴, Hizawa N⁵, Nakagawa H, Sato S⁶, Mushiroda T³, Saeki H¹, Tamari M, Okada Y^{1,3}** (¹Osaka Univ, ²Teijin Pharma LTD, ³RIKEN, ⁴Tokyo Medical and Dental Univ, ⁵Tsukuba Univ, ⁶Tokyo Univ, ⁷Nippon Medical School). Variants at HLA-A, HLA-C, and HLA-DQB1 confer risk of psoriasis vulgaris in Japanese. *J Invest Dermatol.* 2018; **138**: 542-8.
- Kanazawa J¹, Masuko H¹, Yamada H¹, Yatagai Y¹, Sakamoto T¹, Kitazawa H¹, Iijima H², Naito T², Hirota T, Tamari M, Hizawa N¹** (¹Tsukuba Univ, ²Tsukuba Medical Center). How important is allergic sensitization as a cause of atopic asthma? *Allergol Int.* 2018; **67**: 292-4.
- Dahlin A¹, Qiu W¹, Litonjua AA¹, Lima JJ², Tamari M, Kubo M³, Irvin CG⁴, Peters SP⁵, Wu AC¹, Weiss ST^{1,6}, Tantisira KG^{2,4}** (¹Brigham and Women's Hospital and Harvard Medical School, ²Nemours Clinic, ³RIKEN, ⁴Univ of Vermont, ⁵Wake Forest Univ, ⁶Partners Health Care). The phosphatidylinositide 3-kinase (PI3K) signaling pathway is a determinant of zileuton response in adults with asthma. *Pharmacogenomics J.* Epub 2018 Jan 3.
- Chida T¹, Ito M¹, Nakashima K¹, Kanegae Y, Aoshima T¹, Takabayashi S¹, Kawata K¹, Nakagawa Y², Yamamoto M³, Shimano H², Matsuura T, Kobayashi Y, Suda T¹, Suzuki T¹** (¹Hamamatsu University School of Medicine, ²Tsukuba Univ, ³Osaka Univ). Critical role of CREBH-mediated induction of transforming growth factor β 2 by hepatitis C virus infection in fibrogenic responses in hepatic stellate cells. *Hepatology.* 2017; **66**: 1430-43.
- Okii H¹, Yazawa T¹, Baba Y¹, Kanegae Y, Sato H², Sakamoto S¹, Goto T¹, Saito F¹, Kurahashi**

K¹ (¹*Yokohama City Univ Graduate School of Medicine*, ²*Tokyo Univ*). Adenovirus vector expressing keratinocyte growth factor using CAG promoter impairs pulmonary function of mice with elastase-induced emphysema. *Microbiol Immunol*. 2017; **61**: 264-71.

Reviews and Books

Tamari M, Hirota T. Genome-wide association study for atopic dermatitis in the Japanese population. In: Katayama I, Murota H, Satoh T, eds. *Evolution of Atopic Dermatitis in the 21st Century*. Singapore: Springer Singapore, 2018, p45-58.