Project Leader **Takachika Hiroi** Allergy and Immunology Project

Allergy and Mucosal Immunology:

Investigating molecular mechanisms of sublingual immunotherapy (SLIT) and developing therapeutic biomarkers for allergic diseases.

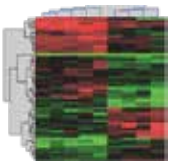
Japanese cedar pollen allergy is the major allergic disease in Japan, and the approximately 35% of Japanese people are affected. In recent years, sublingual immunotherapy has been recognized as an effective curative treatment for the allergic diseases.

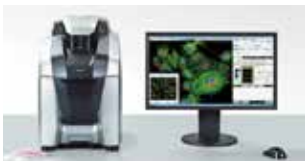
However, the molecular mechanisms of mucosal tolerance still remain unclear. In our laboratory, we focus on the following subjects.

"We are developing new diagnostics and treatments for allergies."

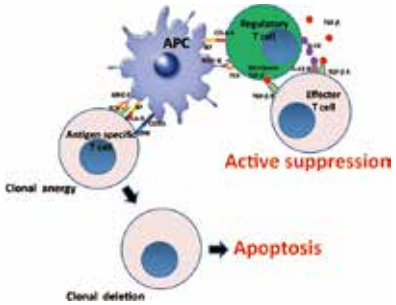
1. Search for effective biomarkers of SLIT

- CNVs
- SNPs
- Epigenome
- Proteome, etc.





2. Elucidation of molecular mechanisms to induce immunological tolerance by SLIT



- iTregs
- Apoptosis
- CTLA-4
- TGF-β
- IL-10 etc.

Gotoh M, Kaminuma O, Nakaya A, Katayama K, Motoi Y, Watanabe N, Saeki M, Nishimura T, Kitamura N, Yamaoka K,Okubo K, and Hiroi T. (2017) "Identification of biomarker sets for predicting the efficacy of sublingual immunotherapy against pollen-induced allergic rhinitis." ***International Immunology*** 29: 291-300.

Nishimura T, Kaminuma O, Saeki M, Kitamura N, Matsuoka K, Yonekawa H, Mori A, and Hiroi T. (2016) "Essential contribution of CD4+ T cells to antigen-induced nasal hyperresponsiveness in experimental allergic rhinitis." ***PLOS ONE*** 11: e0146686.

Yokoyama S, Takada K, Hirasawa M, Perera LP, and Hiroi T. (2011) "Transgenic mice that overexpress human IL-15 in enterocytes recapitulate both B and T cell-mediated pathologic manifestations of celiac disease." ***J. Clin. Immunol.*** 31: 1038-1044.

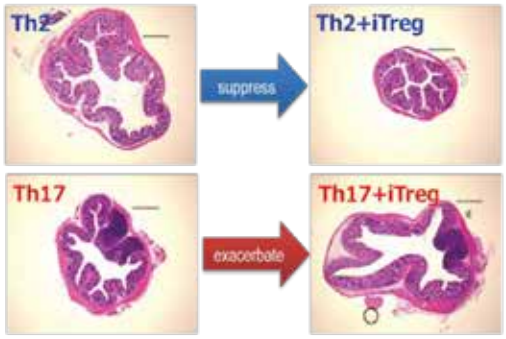
Kaminuma O, Kitamura F, Miyatake S, Yamaoka K, Miyoshi H, Inokuma S, Tatsumi H, Nemoto S, Kitamura N, Mori A, and Hiroi T. (2009) "T-box 21 transcription factor is responsible for distorted TH2 differentiation in human peripheral CD4+ T cells." ***J. Allergy Clin. Immunol.*** 123: 813-823.

Yokoyama S, Watanabe N, Sato N, Filkoski L, Tanaka T, Miyasaka M, Waldmann TA, Hiroi T, and Perera PL. (2009) "Antibody-mediated blockade of IL-15 signaling reverses autoimmune intestinal damage in a mouse model of celiac disease." ***Proc. Natl. Acad. Sci. USA*** 106: 15849-15854.

Allergy and Immunology

Current Topics of Another Research

1. Antigen-specific iTreg cells stimulate Th17-mediated colon inflammation



CD4⁺ helper T cells play a crucial role in allergy and autoimmune diseases including inflammatory bowel diseases (IBDs). Th17 cells and Foxp3⁺ regulatory T cells (Tregs) are thought to promote and suppress inflammatory responses, respectively. Recently we have developed an antigen-specific and organ-targeted inflammation model by transferring antigen-specific helper T cell subsets followed by antigen administration. By adopting this strategy to colon, we have shown that antigen-specific Tregs stimulate Th17-mediated inflammation in a CTLA4-dependent manner. This finding will call for reconsideration of Treg/CTLA4-based immunological modulation to suppress or treat inflammatory diseases.

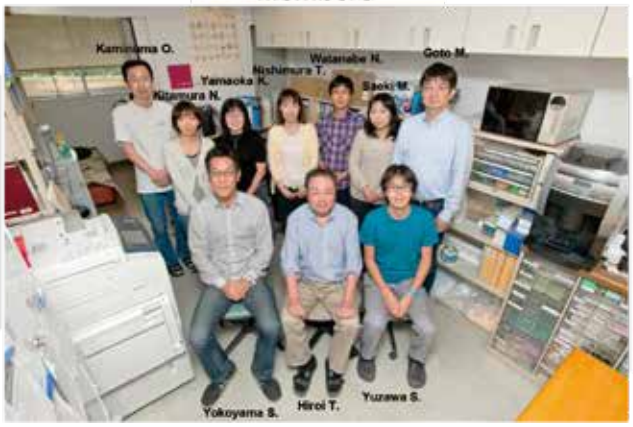
(Watanabe N, et al. (2016) *PLOS ONE*, 11: e0150244.)

2. The mechanisms of allergic inflammation investigated using "cloned mice" of antigen-specific CD4⁺ T cells

Allergens bind to a T-cell receptor (TCR) on CD4⁺ T cells and induce a series of immune reaction. TCR-transgenic mice are important tools to analyze antigen-response mechanisms, but their non-endogenous TCR might induce immune responses in a manner distinct from those induced by the endogenous TCR. Cloning by the nuclear transfer method enables us to produce animals that retain the donor genotypes in all tissues including germline and immune systems. We generated cloned mice carrying TCR genes of antigen-specific CD4⁺ T cells that have rearranged in an endogenous manner. These cloned mice express antigen-specific TCR under the intrinsic promoter, and present a unique animal model with which one can investigate CD4⁺ T cell-mediated pathogenesis and cellular commitment in immune diseases.

(Kaminuma O, et al. (2017) *EMBO Rep.* 18: 885-93.)

Members



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