

## Research Center for Medical Sciences

### Division of Molecular Immunology

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#### General Summary

Our research interests have focused on the analysis of the basic immune system, which protects us from a number of diseases, and of immune disorders, such as hypersensitivity diseases and autoimmune diseases.

#### Research Activities

##### *Involvement of interleukin 31 receptor A in morphine-induced itching and antinociception in mice*

Morphine is an effective analgesic for the treatment of severe pain, but it can cause itching in patients. The present study examined the possible involvement of interleukin (IL) 31 receptor A (IL-31RA) in morphine-induced itching and antinociceptive effects in IL-31RA-deficient mice and wild-type mice. The present findings suggest that IL-31RA plays a significant role, perhaps in sensory neurons or the spinal cord or both rather than in the brain, in the modulation of morphine-induced itching and antinociception. Here, we have demonstrated that IL-31RA is a possible common mediator of itching and the antinociception of morphine. Therefore, IL-31RA might be a noteworthy target for considering the novel mechanism of itch and pain signaling affected by morphine.

##### *Evaluation of basophil activation caused by transgenic rice seeds expressing whole T-cell epitopes of the major Japanese cedar pollen allergens*

Japanese cedar (JC) pollinosis is a serious type I allergic disease in Japan. Although subcutaneous immunotherapy and sublingual immunotherapy have been used to treat JC pollinosis, high doses of allergens might cause immunoglobulin E-mediated allergic reactions. Developed as candidates for oral immunotherapy are transgenic rice seeds that contain genetically modified Cry j 1 and Cry j 2, the 2 major allergens of JC pollen. To verify the allergenic safety of transgenic rice seeds, we investigated with the basophil activation test the percentage of activated basophils induced by transgenic rice seed extract. Blood samples were collected from 29 patients with JC pollinosis. Transgenic rice seed extract, nontransgenic wild-type rice seed extract, and Cry j 1 and Cry j 2 were mixed with the blood via reagents. The percentage of activated basophils was assessed via the expression of CD203c, a basophil activation marker.

The percentage of activated basophils after stimulation with transgenic rice seed extract was significantly lower than that induced by the mixture of Cry j 1 and Cry j 2. Transgenic rice seed extract caused little activation of basophils in patients with JC pollinosis compared with that induced by the mixture of Cry j 1 and Cry j 2. Furthermore, the per-

centage of activated basophils did not differ significantly between transgenic rice seed extract and wild-type rice seed extract.

Regarding the risk of immunoglobulin E-mediated allergic reactions, the results show that transgenic rice seeds would be much safer than conventional immunotherapies with crude antigens, including Cry j 1 and Cry j 2, and might be as safe as wild-type rice seeds.

*Development of vaccination to induce cytotoxic T lymphocytes against tumor-specific antigens*

A vaccine that raises specific cytotoxic T cells against tumors or pathogens is the convincing approach to overwhelm these diseases. On the basis of a previous study, we have developed a new liposome-based adjuvant to induce cytotoxic T lymphocytes (CTLs) by mixing protein antigens and adjuvant before administration. To use this vaccine to treat cancer, further analysis was carried out, and these vaccine-induced helper T type 1 cells efficiently shifted the immune response, but inducing CTLs against cancer was difficult. To prime CTL induction, we compared several candidates for suicide gene therapy. With suicide gene therapy against colon tumors, an efficient tumor vaccine was acquired to reject 1 million tumor cells implantation. Also, the cryoimmunization of tumor expression ovalbumin as a reporter was confirmed to have induced specific CTLs. With these results, we are developing a vaccine to induce CTLs to suppress tumor recurrence.

**Publications**

**Tsuji M<sup>1</sup>, Arai I, Miyagawa K<sup>1</sup>, Miyagishi H<sup>1</sup>, Saito A<sup>1</sup>, Takeda K<sup>1</sup>, Takeda H, Akiyama N, Saito S (IUHW).** Involvement of interleukin-31 receptor A in morphine-induced itching and antinociception in mice. *Eur J Pain.* 2019; **23**: 378-88.

**Takaishi S, Saito S, Kamada M, Otori N,**

**Kojima H, Ozawa K<sup>1</sup>, Takaiwa F<sup>1</sup> (NARO).**

Evaluation of basophil activation caused by transgenic rice seeds expressing whole T cell epitopes of the major Japanese cedar pollen allergens. *Clin Transl Allergy.* 2019; **9**: 11. <https://doi.org/10.1186/s13601-019-0249-8>.