

Japan Academy Prize to:

Shimon SAKAGUCHI
 Professor, Immunology Frontier Research
 Center, Osaka University

for “Control of Immune Responses by
 Regulatory T Cells”

**Outline of the work:**

Dr. Shimon Sakaguchi's main contribution to immunology is his discovery of regulatory T (Treg) cells and elucidation of the molecular and cellular basis of their development and function in disease and healthy states.

Dr. Sakaguchi discovered in 1995 a subpopulation of T cells that was naturally present in the normal immune system, constituting approximately 5% of T cells, and specialized for immunosuppression. He named the population as Treg cells and showed that removal of the population from normal animals elicited spontaneous development of a spectrum of autoimmune diseases immunopathologically similar to the human counterparts (such as type 1 diabetes, autoimmune thyroiditis, and autoimmune arthritis). This was a clear demonstration that Treg cells are engaged in the maintenance of natural self-tolerance and their dysfunction can be a direct cause of autoimmune diseases. He subsequently demonstrated that reduction of Treg cells was able to elicit effective cancer immunity while enhancement of Treg-mediated suppression can induce tolerance to organ transplants. His group then showed in 2003 that Treg cells were specifically expressing the transcription factor Foxp3. This is a direct demonstration that natural Treg cells play a crucial role in immunological self-tolerance and homeostasis in humans because mutations of the Foxp3 gene impair Treg development/function, and cause human genetic diseases called IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome, which is characterized by autoimmune diseases such as type 1 diabetes and thyroiditis, inflammatory bowel disease, and severe allergy. Dr. Sakaguchi has analyzed how Foxp3 controls Treg cell function and development, and also extended his research to the analysis of human Foxp3⁺ Treg cells. He has shown that human Foxp3⁺ T cells can be dissected into subpopulations, whose numerical and functional changes bear a good correlation with pathophysiology of immunological disorders. His recent contribution to human immunology is the characterization of cancer antigens in adult T cell leukemia/lymphoma, which is induced by HTLV-1 (human T-lymphotropic virus-1) endemic in Japan, as malignant transformation of human Treg cells.

Based on Dr. Sakaguchi's research accomplishments, Treg cells are now under active investigation in laboratories and clinics all over the world to apply them for the treatment and prevention of immunological diseases and also control of a variety of physiological and pathological immune responses as in the setting of autoimmunity, tumor immunity, organ transplantation, microbial immunity, allergy, and feto-maternal tolerance.

Representative publications:

1. Sakaguchi, S., Fukuma, K., Kuribayashi, K., and Masuda, T. Organ-specific autoimmune disease induced in mice by elimination of T-cell subset. I. Evidence for active participation of T cells in natural self-tolerance; deficit of a T-cell subset as a possible cause of autoimmune disease. *J. Exp. Med.* 161:72-87, 1985.
2. Sakaguchi, S., Sakaguchi, N., Asano, M., Itoh, M., and Toda, M. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor α -chains (CD25): breakdown of a single mechanism of immunologic self-tolerance causes various autoimmune diseases in mice. *J. Immunol.* 155:1151-1164, 1995.

3. Asano, M., Toda, M., Sakaguchi, N., and Sakaguchi, S. Autoimmune disease as a consequence of developmental abnormality of a T-cell subpopulation. *J. Exp. Med.* 184: 387-396, 1996.
4. Shimizu, J., Yamazaki, S., Takahashi, T., Ishida, Y., and Sakaguchi, S. Stimulation of CD25⁺ CD4⁺ regulatory T cells through GITR breaks immunological self-tolerance. *Nat Immunol.* 3: 135-142, 2002.
5. Hori, S., Nomura, T., and Sakaguchi, S. Control of regulatory T cell development by the transcription factor Foxp3. *Science.* 299: 1057-1061, 2003.
6. Sakaguchi, N., Takahashi, T., Hata, H., Nomura, T., Tagami, T., Yamazaki, S., Sakihama, T., Matsutani, T., Negishi, I., Nakatsuru, S., and Sakaguchi, S. Altered thymic T-cell selection due to a mutation of the ZAP-70 gene causes autoimmune arthritis in mice. *Nature.* 426: 454-60, 2003.
7. Setoguchi, R., Hori, S., Takahashi, T., and Sakaguchi, S. Homeostatic maintenance of natural Foxp3⁺ CD25⁺ CD4⁺ regulatory T cells by interleukin (IL)-2 and induction of autoimmune disease by IL-2 neutralization. *J. Exp. Med.* 201: 723-735, 2005.
8. Ono, M., Yaguchi, H., Ohkura, N., Kitabayashi, I., Nagamura, Y., Nomura, T., Miyachi, Y., Tsukada, T., Sakaguchi, S. Foxp3 controls regulatory T cell function via interacting with AML1/Runx1. *Nature.* 446: 685-689, 2007.
9. Wing, K., Onishi, Y., Prieto-Martin, P., Yamaguchi, T., Miyara, M., Fehervari, Z., Nomura, T., and Sakaguchi, S. CTLA-4 control over Foxp3⁺ regulatory T cell function. *Science.* 322: 271-275, 2008.
10. Miyara, M., Shima, T., Kitoh, A., Yoshioka, Y., Niwa, A., Taffin, C., Heike, T., Valeyre, D., Mathian, A., Nakahata, T., Yamaguchi, T., Nomura, T., Wing, K., Ono, M., Amoura, Z., Gorochoy, G., and Sakaguchi, S. Functional delineation and differentiation dynamics of human CD4(+) T cells expressing the FoxP3 transcription factor. *Immunity.* 30: 899-911, 2009.