Press Release

Keio University

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Keio University School of Medicine

Converting “disease-causing T cells” into antigen-specific regulatory T cells —a novel antigen-specific cell therapy for autoimmune disease pemphigus vulgaris—

A research group at the Keio University School of Medicine has developed a novel antigen-specific immunotherapy for the autoimmune disease pemphigus vulgaris (PV). The group was led by Professor Masayuki Amagai (Director, RIKEN IMS), Associate Professor Hayato Takahashi, and Research Fellow Miho Mukai of the Department of Dermatology, Keio University School of Medicine, in collaboration with Professor Shimon Sakaguchi and Associate Professor Norihisa Mikami (Regcell Co., Ltd.) of the University of Osaka.

Using an induction method originally developed at the University of Osaka (1), the team successfully converted disease-causing T cells into stable and functional induced regulatory T cells (S/F-iTregs) that specifically recognize desmoglein 3 (Dsg3)—the autoantigen responsible for PV. In a mouse model, treatment with these Dsg3-specific S/F-iTregs markedly reduced disease severity and autoantibody levels, demonstrating precise, antigen-specific immune suppression. Importantly, the researchers also generated similar S/F-iTregs from the peripheral blood T cells of patients with pemphigus vulgaris not by genetic engineering, but through pharmacological and epigenetic reprogramming that stabilizes Foxp3 expression and confers durable regulatory function. These patient-derived S/F-iTregs effectively suppressed T-cell proliferation in vitro, demonstrating their therapeutic potential.

This study establishes a foundation for next-generation, antigen-specific, and non-genetic cell therapy for autoimmune diseases, providing a new approach to reprogram disease-causing T cells into stable, antigen-specific regulatory cells with high safety and precision.

These findings were published online in the international journal *Science Translational Medicine* on October 22, 2025 (Eastern Standard Time).

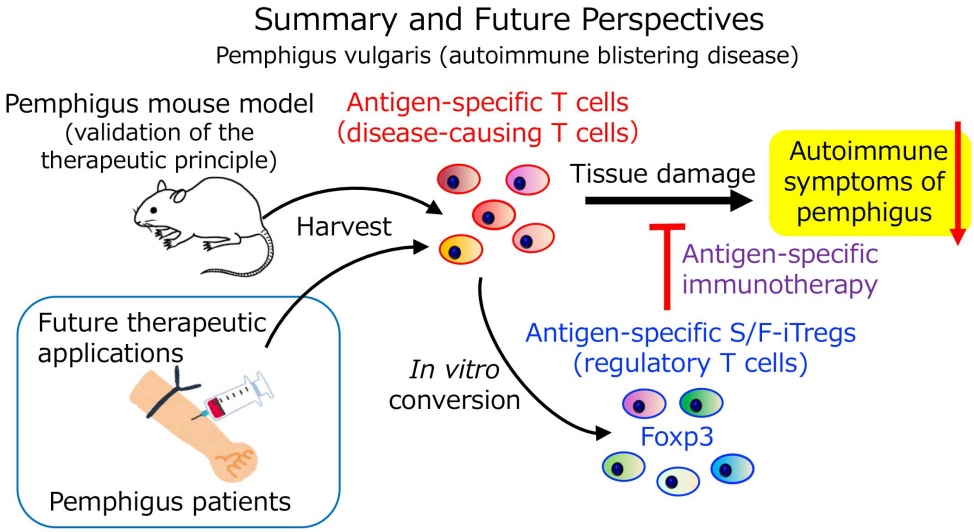

Figure 1. Overview of the study

"Disease-causing" pathogenic T cells were converted into antigen-specific, stable and functional induced regulatory T cells (S/F-iTregs) that is Dsg3-specific in this study. Dsg3-specific S/F-iTregs effectively alleviated pemphigus–like symptoms in mice in an antigen-specific manner. Looking ahead, Dsg3-specific S/F-iTregs converted from peripheral blood T cells of patients with pemphigus vulgaris are also expected to exert similar antigen-specific therapeutic effects as observed in the mouse model.

1. Research Background

Tregs act as the "brakes" of the immune system. Normally, our immune system protects the body by attacking harmful invaders such as bacteria and viruses. However, it can sometimes overreact and damage our own tissues, triggering an autoimmune response. Tregs suppress such excessive immune activity and help prevent autoimmune diseases and allergies.

Although Tregs can be expanded in the laboratory, their properties tend to be unstable, making it difficult to use them as a therapeutic option. Researchers at the University of Osaka have developed a method to generate S/F- iTregs, which has now been successfully completed (Reference 1), marking a major step toward clinical application.

Pemphigus vulgaris is an autoimmune blistering disease in which autoantibodies are produced against desmoglein 3 (Dsg3)—a protein critical for cell adhesion between skin keratinocytes. This results in the formation of blisters across the body.

In this study, the researchers demonstrated that Dsg3-specific S/F-iTregs, which recognize the disease-related antigen, proliferated in mice with skin inflammation and expressed higher levels of molecules important for Treg-mediated immune suppression than wild-type (WT) S/F-iTregs, which lack specificity for a particular antigen. Administration of these Dsg3-specific S/F-iTregs to pemphigus model mice reduced both skin symptoms and anti-Dsg3 antibody titers, confirming their therapeutic effect. Furthermore, the team successfully induced S/F-iTregs from peripheral blood T cells of patients with pemphigus vulgaris and demonstrated that these patient-derived S/F-iTregs could suppress T-cell proliferation in vitro, suggesting their potential for future therapeutic use.

2. Research Significance and Future Development

In this study, the researchers first used a method developed at the University of Osaka to generate S/F-iTregs from both WT and Dsg3-specific T cells.
S/F-iTregs derived from either cell type showed higher expression levels of Foxp3, a key protein that defines Treg identity, compared with conventional iTregs (C-iTregs) (Fig. 2).

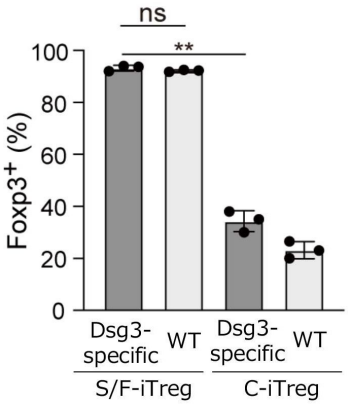

Figure 2. Proportion of Foxp3-positive cells in S/F-iTregs and conventional iTregs
Dsg3-specific S/F-iTregs showed a higher percentage of Foxp3-positive cells compared with Dsg3-specific C-iTregs ($p < 0.01$, ns: not significant).

In natural regulatory T cells (nTregs), the *Foxp3* gene is known to be highly demethylated (Note 4), a feature associated with the stable expression of Foxp3 and function of immunosuppression. While C-iTregs show a lower level of demethylation, the S/F-iTregs induced in this study exhibited a highly demethylated state comparable to that of nTregs (Fig. 3).

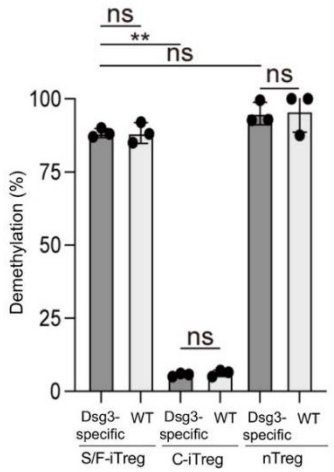

Figure 3. Demethylation status of the Foxp3 gene regulatory region in S/F-iTregs, C-iTregs, and nTregs
Dsg3-specific S/F-iTregs showed a high level of demethylation comparable to that of WT S/F-iTregs, indicating stable Foxp3 gene expression ($p < 0.01$, ns: not significant).

Next, the researchers compared the *in vivo* function of Dsg3-specific S/F-iTregs with that of WT S/F-iTregs, which lack defined antigen specificity.

When each type of S/F-iTreg was transferred into mice with skin inflammation and analyzed two weeks later, the Dsg3-specific S/F-iTregs were found to be more abundant in the skin-draining lymph nodes than WT S/F-iTregs or WT nTregs. These cells also showed higher expression of CTLA-4 and IL-10, molecules that play key roles in the immunosuppressive function of Tregs (Fig. 4).

These findings suggest that, *in vivo*, antigen-specific Tregs proliferate upon recognizing self-antigens (Dsg3 in this study) and exhibit enhanced suppressive activity through the elevated expression of immunoregulatory molecules critical for Treg function.

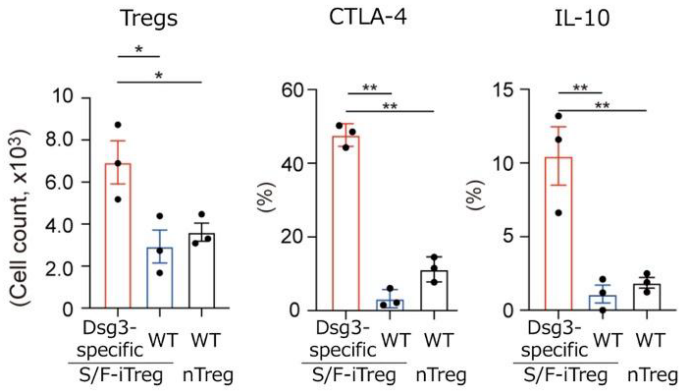

Figure 4. Superior quantitative and qualitative properties of Dsg3-specific S/F-iTregs in skin draining lymph nodes *in vivo*

After transfer into mice, Dsg3-specific S/F-iTregs were found in greater numbers in the skin-draining lymph nodes and showed higher expression of CTLA-4 and IL-10 compared with WT

Next, the researchers tested the therapeutic effects of Dsg3-specific S/F-iTregs in a PV mouse model. In mice that received S/F-iTreg treatment, the number of Dsg3-specific B cells—which directly cause disease—was significantly reduced compared with the control group, while the total number of B cells remained unchanged (Fig. 5).

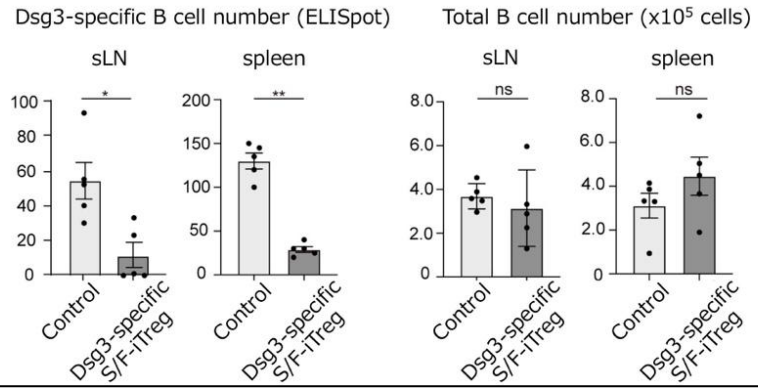

Figure 5. Dsg3-specific and total B cells in the skin-draining lymph nodes and spleen of PVmodel mice

Administration of Dsg3-specific S/F-iTregs to pemphigus model mice suppressed Dsg3-specific B cells but did not affect the total B cell population.

In addition, mice treated with Dsg3-specific S/F-iTregs showed a significant reduction in anti-Dsg3 antibody titers and clinical disease scores compared with the control group without S/F-iTreg treatment ($p < 0.01$, Fig. 6). These findings indicate that, in the PV mouse model, Dsg3-specific S/F-iTregs suppress Dsg3-specific B cells, leading to a reduction in autoantibody production and disease symptoms.

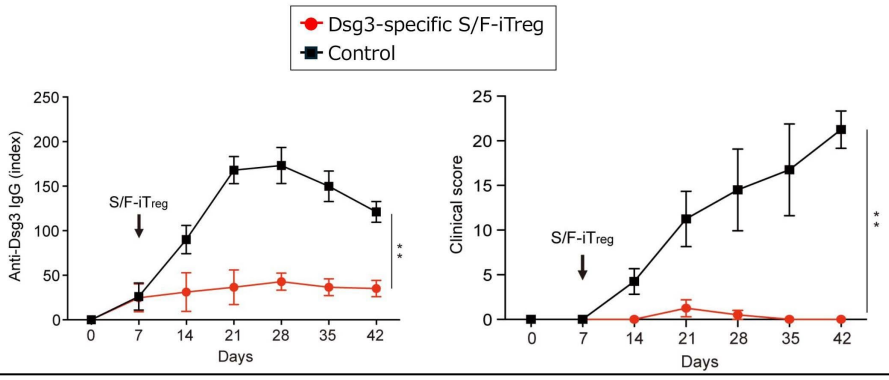

Figure 6. Time course of disease-inducing antibody titers and clinical scores in PV mouse model

In the PV model, Dsg3-specific S/F-iTregs suppressed both anti-Dsg3 antibody titers and clinical disease scores ($p < 0.01$).

Finally, S/F-iTregs were successfully induced from the blood of patients with pemphigus vulgaris. Consistent with the results observed in mice, the patient-derived S/F-iTregs exhibited higher Foxp3 expression and greater Foxp3 gene demethylation compared with C-iTregs. When these S/F-iTregs were co-cultured with peripheral blood $CD4^+$ T cells and stimulated with anti-CD3 antibodies for four days, they effectively suppressed the proliferation of $CD4^+$ T cells (Fig. 7).

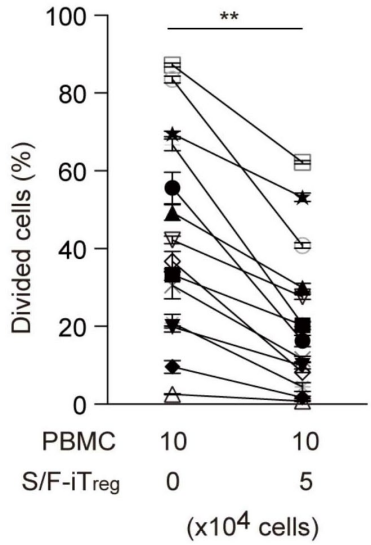

Figure 7. Immunosuppressive effects of S/F-iTregs generated from the peripheral blood of patients with pemphigus vulgaris

The proliferation of peripheral blood $CD4^+$ T cells was significantly suppressed in the presence of S/F-iTregs (right column) compared with cultures without S/F-iTregs (left column).

The stability of Foxp3 expression in Tregs is influenced by an epigenetic modification known as DNA methylation. A research team led by Professor Shimon Sakaguchi at the University of Osaka has established a groundbreaking method to generate S/F-iTregs by promoting demethylation of the Foxp3 gene, thereby ensuring its stable expression (Reference 1).

In autoimmune diseases, disease-causing T cells attack specific self-proteins (autoantigens) in an antigen-dependent manner. Using this new approach, the researchers succeeded in converting disease-causing T cells into regulatory T cells that suppress disease activity without any genetic engineering, while maintaining their original antigen specificity. This enables a new form of antigen-specific immune suppression that selectively targets only the immune reactions responsible for the disease.

Conventional treatments for autoimmune diseases often suppress the entire immune system, leading to unwanted side effects such as the risk of infection. In contrast, the antigen-specific suppression demonstrated

in this study acts only on immune cells that recognize the disease-causing self-antigen, while leaving protective immune functions intact. This represents a new and safer therapeutic strategy that can effectively control disease symptoms while minimizing side effects. Building on these findings, researchers are now preparing for clinical application of this approach to develop antigen-specific cell therapies for autoimmune diseases.

3. Notes

This study was supported by the Practical Research Project for Rare/Intractable Diseases "Development of cell therapy for pemphigus vulgaris using functionally-stabilized autologous induced regulatory T cells'' and the LEAP Program for Leading Advanced Projects for Medical Innovation—Incubation-Type ''Study of immunoregulatory technology targeting regulatory T cells'' from the Japan Agency for Medical Research and Development (AMED); by a Health and Labor Sciences Research Grant for Research on Intractable Diseases (23FC1039) from the Ministry of Health, Labour and Welfare of Japan; by JSPS KAKENHI Grant Numbers JP19H01051, JP24H00634; by the Keio Gijuku Academic Development Fund; and by a research grant from the LEO Foundation.

4. Research Paper

Title: Conversion of pathogenic T cells into functionally stabilized Treg cells for antigen-specific immunosuppression in pemphigus vulgaris
Authors: Miho Mukai, Hayato Takahashi, Yoko Kubo, Yasuhiko Asahina, Hisato Iriki, Hisashi Nomura, Aki Kamata, Hiromi Ito, Yutaka Kurebayashi, Jun Yamagami, Norihisa Mikami, Shimon Sakaguchi, Masayuki Amagai
Publication: *Science Translational Medicine*
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Glossary

- **Regulatory T cells (Tregs):** Regulatory T cells (Tregs) are a subset of $CD4^+$ T cells characterized by the expression of the transcription factor Foxp3, which plays a crucial role in suppressing immune responses. Tregs that are artificially induced from conventional T cells in vitro are referred to as iTregs.
- **Pemphigus vulgaris (PV):** A life-threatening, organ-specific autoimmune disease characterized by blistering and erosion of the skin and mucous membranes. It is caused by pathogenic IgG autoantibodies directed against desmoglein 3 (Dsg3), a cell adhesion molecule in the epidermis.
- **Method for generating stabilized iTregs:** Conventional iTregs are typically induced from $CD4^+$ T cells by stimulating both CD3 and CD28 molecules. In contrast, the new method used in this study omits CD28 stimulation and instead applies repeated stimulation in the presence of specific compounds, vitamin C, and other factors, enabling the generation of iTregs that maintain high Foxp3 expression and a high degree of DNA demethylation—features defining stable and functional iTregs (S/F-iTregs).
- **Natural regulatory T cells (nTregs):**
  Tregs that are generated naturally within the body are referred to as nTregs. They maintain immune homeostasis by controlling the activity of other immune cells. Key immunoregulatory genes, such as *Foxp3*, exist in a demethylated state, conferring functional stability to these cells.
- **Demethylation:** DNA within our genes can be modified by the addition of small chemical tags called methyl groups, which function as "on/off switches" for gene activity. Methylated genes are typically silenced. Demethylation refers to the removal of these methyl groups, making the gene more transcriptionally active.

Reference

1. Generating functionally stable and antigen-specific Treg cells from effector T cells for cell therapy of inflammatory diseases: Mikami, N. et al. Science translational medicine, in press (to appear as back-to-back papers).

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